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THE MECHANISM OF MIXED HYDRIDE REDUCTIONS
OF ORGANIC FUNCTIONAL GROUPS

A THESIS

Presented to

The Faculty of the Graduate Division

by

Burgess John Albert Cooke

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THE MECHANISM OF MIXED HYDRIDE REDUCTIONS
OF ORGANIC FUNCTIONAL GROUPS

Approved: _____

Chairman _____

Date Approved by Chairman: Mar 1, 1968

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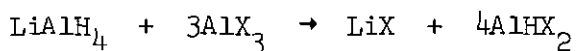
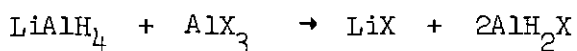
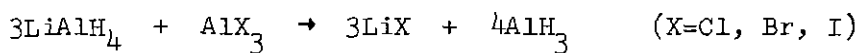
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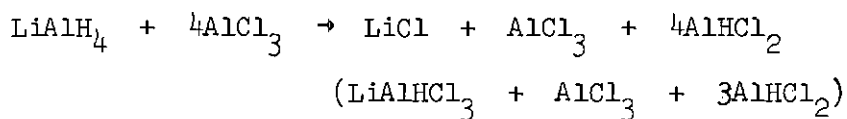
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SUMMARY

A mixed hydride is the name generally given to a reagent produced from the combination of lithium aluminum hydride with some acidic species. The acidic species most commonly used are the aluminum halides, and the reagents resulting from this combination are the various hydridoaluminum halides. This is illustrated in the equations below:



One mixed hydride that has been studied frequently is the reagent produced from the combination of four moles of aluminum chloride to one mole of lithium aluminum hydride. This reagent has been shown to have the following composition:



One of the goals of this project was to determine the role played by each of these species in reductions involving the one to four lithium aluminum hydride to aluminum chloride combination. Another goal was to determine the effect of varying the number and type of halides attached to the central aluminum atom. Since the halides have different electronegativities, and sizes, the stoichiometric amount and the type of halide should have a pronounced effect

on the type of reactivity shown by a mixed hydride; i.e., the more halide present, and the more electronegative the halide, the more Lewis acidity and less reducing power would be exhibited by a mixed hydride reagent. In the case of mixed hydrides with bulky substituents, such as iodide, steric effects might be observed.

Mixed hydride reactions are usually carried out in ether, so that the hydridoaluminum halides exist as diethyl etherates. Other Lewis bases, such as triethylamine and tetrahydrofuran can coordinate with these trivalent aluminum species. Another objective of this work was to determine the effect of varying the solvating species on the type of reactivity exhibited by mixed hydride reagents. Also, the effect of varying the substituents from halide to alkoxide (methoxide, isopropoxide, and t-butoxide) was determined.

A good substrate for studying these effects was found to be 2,4,4-trimethyl-2-pentene oxide. Three reduction products are obtained when this epoxide is treated with a mixed hydride reagent. The ratios of these products are very sensitive to the type of mixed hydride used. The product ratios were determined by analysis using vapor phase chromatography. These products are 2,4,4-trimethylpentanol-2, 2,4,4-trimethylpentanol-3, and tetramethylbutanol. The first two are largely the product of direct reduction, and the third is the product of a t-butyl shift and subsequent reduction. A predominance of the latter product over the former two would indicate that the mixed hydride used is a relatively strong Lewis acid, and consequently, a relatively weak reducing agent.

The following results were obtained from our study:

In reductions involving the reagent formed by combining one mole of lithium aluminum hydride with four moles of aluminum chloride, it appears that the excess aluminum chloride present plays no role in determining the product ratios. However, the lithium chloride which is presumably complexed either with the hydridoaluminum chloride or the aluminum chloride does affect the type of reactivity exhibited by this reagent. The lithium chloride-hydridoaluminum dichloride complex is evidently a stronger reducing agent than is hydridoaluminum dichloride alone.

The effects outlined above were observed when the type and number of attached halide atoms were varied. Steric effects were almost always very small or apparently nonexistent in the mixed hydride. A mixed hydride solvated by a more basic, or a more strongly electron donating substance, should be a weaker Lewis acid and consequently, a stronger reducing agent than the same hydride as the diethyl etherate. The two bases studied in this work were tetrahydrofuran and triethylamine. The expected reactivity differences between mixed hydrides as tetrahydrofuranates and the corresponding reagents as diethyletherates were observed. The results from the reductions involving mixed hydrides as triethylamminates can not be simply interpreted on the basis of electronic effects, presumably because of the considerable steric bulk of triethylamine relative to that of diethyl ether and tetrahydrofuran.

The following results were obtained from the reductions involving the alkoxyaluminum hydrides. First of all, β -diisobutylene oxide is

fairly inert to these reagents. In most cases, reaction between epoxide and the hydrides in question did not occur to a significant extent. It appears that alkoxyaluminum hydrides exhibit only negligible Lewis acidity, and consequently little reactivity toward the bulky β -diisobutylene oxide. Therefore, no unequivocal statements can be made about the types of reactivity exhibited by these reagents. More work needs to be done with reductions involving these hydrides, with some less sterically hindered epoxide, such as styrene oxide.

CHAPTER I

INTRODUCTION AND HISTORICAL BACKGROUND

Since its discovery in 1946^{1,2} lithium aluminum hydride has become one of the most widely used reagents in the field of organic chemistry. It is a very potent reducing agent and will hydrogenate almost any polar, unsaturated functional group. The table below illustrates the wide applicability of these reductions for synthetic work.

Various attempts have been made to alter the properties of lithium aluminum hydride such that the resulting substance will be a less reactive and more selective reducing agent. The most widely known of these experiments concerns the work of H. C. Brown on the lithium alkoxyaluminumhydrides. If tert-butanol^{3,4} or methanol⁴ is added to lithium aluminum hydride in diethyl ether, tetrahydrofuran or diglyme the corresponding lithium mono-, di- or trialkoxyaluminumhydrides are produced. The reactions are stepwise and the products are dependent on the ratio of alcohol to hydride. An equivalent amount of hydrogen is liberated.

1. A. E. Finholt, A. C. Bond, H. I. Schlesinger, J. Am. Chem. Soc., 69, 1199 (1947).

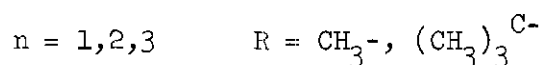
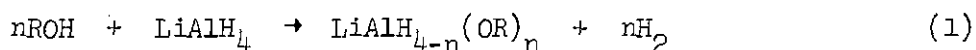
2. R. F. Nystrom and W. G. Brown, J. Am. Chem. Soc., 69, 1197 (1947).

3. H. C. Brown and R. F. McFarlin, J. Am. Chem. Soc., 78, 252 (1956).

4. H. C. Brown and C. J. Shoaf, ibid., 86 1079 (1964).

Table 1.⁵ Functional Groups Reduced by Lithium Aluminum Hydride

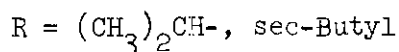
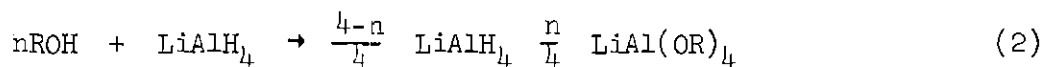
Functional Group	Product
Aldehyde	Primary alcohol
Ketone	Secondary alc.
Quinone	Hydroquinone
Epoxide	Alcohol
Ester	Alcohol
Lactone	Diol
Carboxylic Acid	1 alcohol
Anhydride	1 alcohol
Amide, 1°	Amine, 1°
Amide, 2°	Amine, 2°
Amide, 3°	Amine, 3°
Nitrile	1° Amine or Aldehyde
Nitro (aryl)	Azo compound
Nitro (alkyl)	Amine
Azoxy	Azo compound
Anil	Amine
Nitroso	Azo compound
Acid chloride	1° alc.
Alkyl halide	Hydrocarbon
Disulfide	Thiol
Sulfoxide	Sulfide
Sulfonyl chloride	Thiol



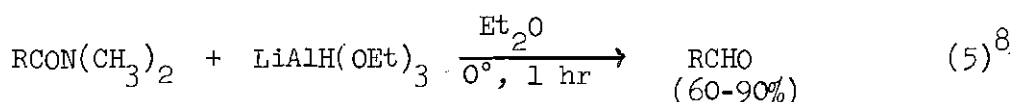
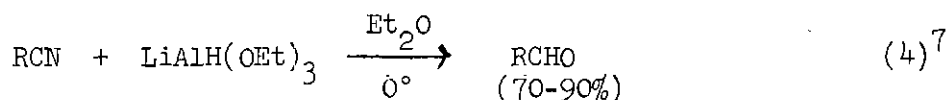
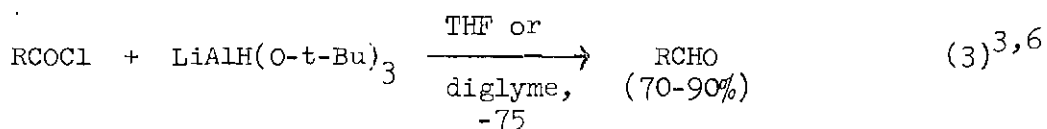
Is isopropyl or sec-butyl alcohol⁴ is used, the intermediate lithium alkoxyaluminumhydrides evidently disproportionate to the corresponding lithium tetraalkoxyaluminumhydrides and lithium aluminum

5. W. G. Brown, "Organic Reactions," R. Adams, ed., J. Wiley and Sons, Inc., New York, Vol. 6, 1956.

hydride.



The modified reducing power and synthetic utility of some of the lithium alkoxyaluminumhydrides are illustrated by the equations below:



The reactions above can be considered to be quite general since the authors carried them out on twenty-five or thirty compounds. These reactions compared favorably^{7,8} in yield with older synthetic methods, and in some cases represented an improvement (eq. 3).^{3,6}

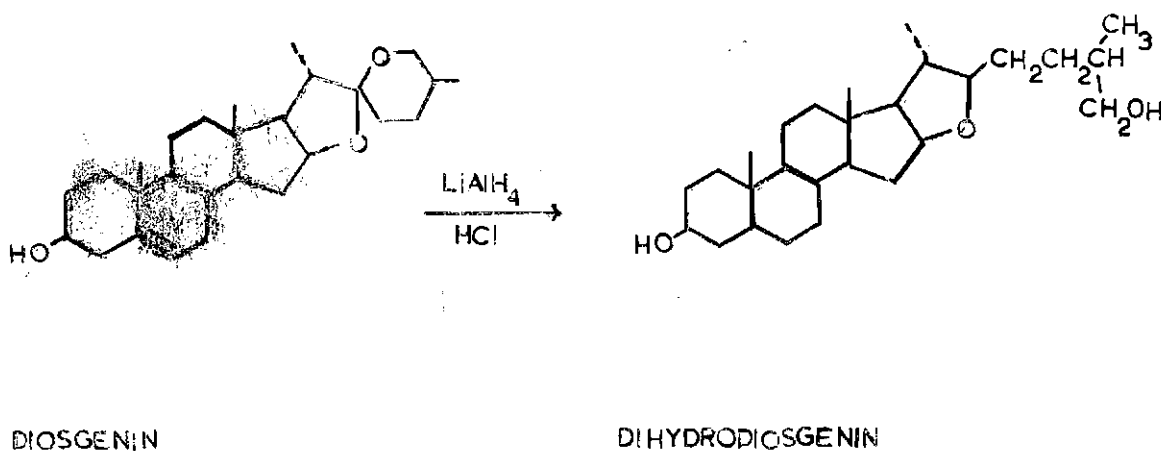
6. H. C. Brown and R. F. McFarlin, J. Am. Chem. Soc., 80, 5372 (1958).

7. H. C. Brown and C. P. Garg, ibid., 86, 1085 (1964).

8. H. C. Brown and A. Tsukamoto, ibid., 86, 1089 (1964).

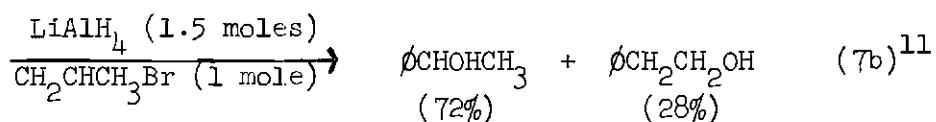
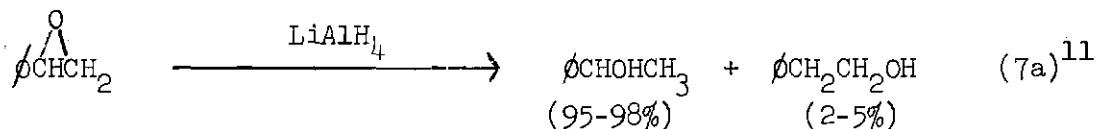
When lithium aluminum hydride is allowed to react with certain strongly acidic species, a reducing agent is obtained which exhibits a significantly different type of reactivity than that of lithium aluminum hydride reagents. It is with these reagents and their mechanisms of reaction with organic compounds that this work is concerned. In order to better understand the significance of the work described, the historical development and utility of these reagents, as well as their nature and modes of reaction with organic functional groups, will now be discussed.

Doukas and Fontaine⁹ found that the reagent formed by adding solid lithium aluminum hydride to an ethereal solution of hydrogen chloride would perform the following conversion:

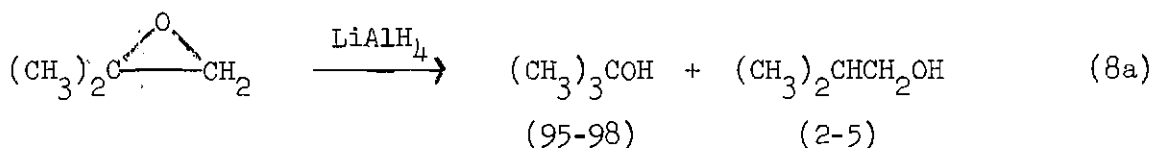


9. H. M. Doukas and T. D. Fontaine, *ibid.*, 75, 5355 (1953).

If lithium aluminum hydride or the hydrogen halides¹⁰ are used alone, the above reaction does not occur. The addition of allyl bromide (which probably functions as a donor of bromides to the reaction medium) to lithium aluminum hydride produces a reagent with similar properties:¹¹



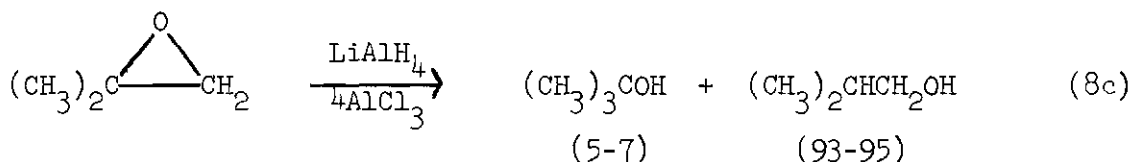
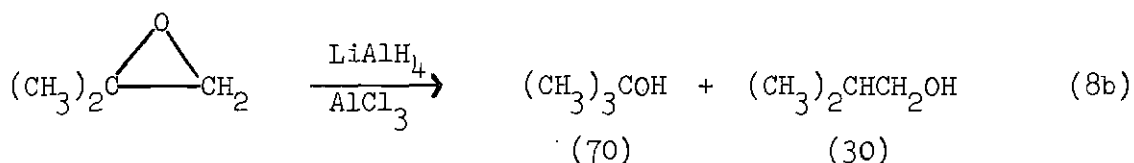
Finally, it was found that addition of aluminum chloride or bromide to lithium aluminum hydride produced similar results. Furthermore it was found that the stoichiometric ratio of hydride to halide in the mixed hydride reagent could have a pronounced effect on the product distributions in the reduction of certain epoxides:^{11,12}



10. E. L. Eliel, V. G. Badding, M. N. Rerick, *ibid.*, 82, 1362 (1960).

11. E. L. Eliel and M. N. Rerick, *ibid.*, 82, 1362 (1960).

12. E. L. Eliel and D. W. DelMonte, *ibid.*, 80, 1744 (1958).



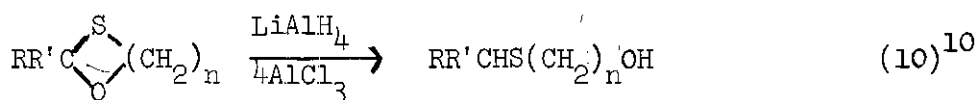
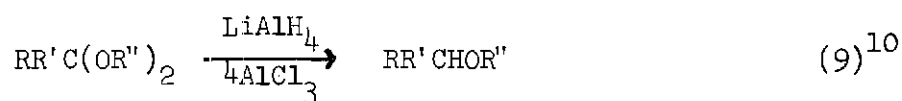
The addition of lithium aluminum hydride to aluminum halides seems to be the currently accepted method for generating a mixed hydride reagent.¹³ The reagents generated by mixing lithium aluminum hydride and aluminum chloride in molar ratios of one to four, three to one, and one to one have received the most attention. The one to four reagent gives optimum yields in some of the conversions shown below.^{13,10,14} (In fact, some workers in the field refer to the one to four reagent as the mixed hydride reagent.^{13,15} Others are not so specific.¹⁶)

13. E. L. Eliel, Rec. Chem. Prog., 23, 129 (1961).

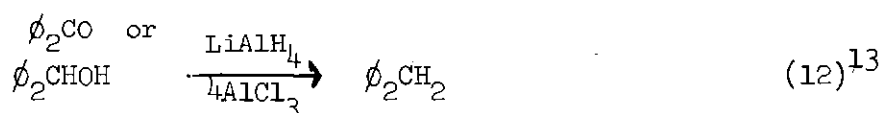
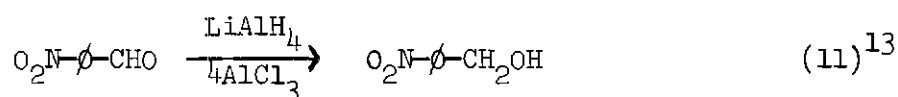
14. E. L. Eliel, J. A. Pilato, V. G. Badding, J. Am. Chem. Soc., 84, 2377 (1962).

15. E. C. Ashby and J. Prather, ibid., 87, 1748 (1966).

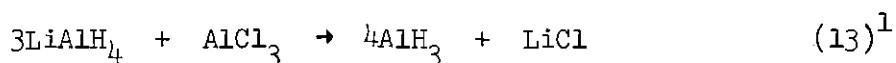
16. P. T. Lansbury and V. A. Pattison, Tet. Letters, 1966, 3073.



$$n = 2, 3$$



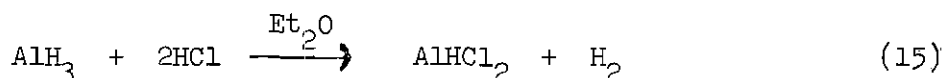
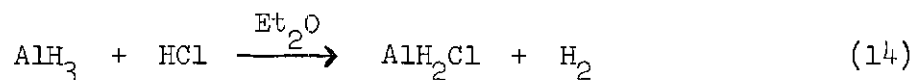
In order to understand how mixed hydride reductions take place, it is important to know the inorganic chemistry involved when halide donors are combined with lithium aluminum hydride. When lithium aluminum hydride and aluminum chloride are mixed in a three to one molar ratio, aluminum hydride and lithium chloride are produced.



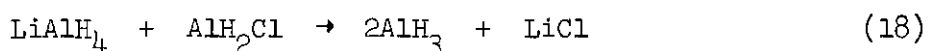
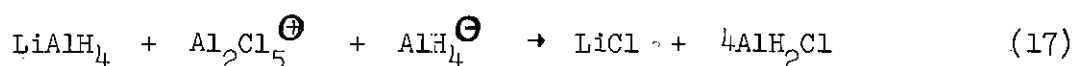
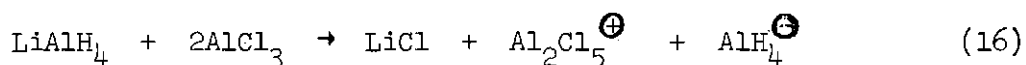
Lithium chloride precipitates immediately, and aluminum hydride polymer precipitates after a short period of time. Wiberg¹⁷ found that when

17. E. Wiberg and K. Modritzner, R. Uson Lacal, Rev. Acad. Sci. Exact. Fis. Quim. Y. Nat. Zarazoga, 9, 91 (1954).

aluminum hydride is allowed to react with hydrogen chloride in ether, hydridoaluminum halides are formed according to the following equations:



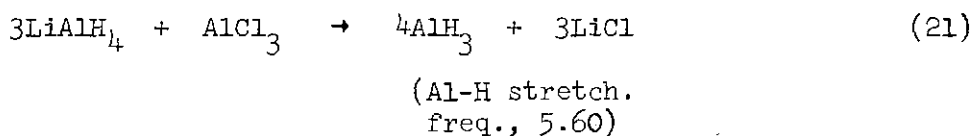
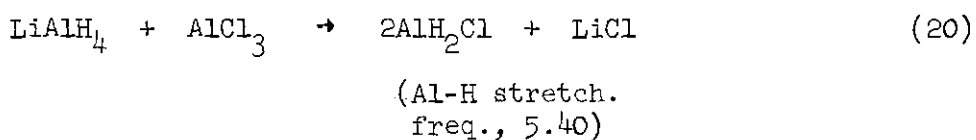
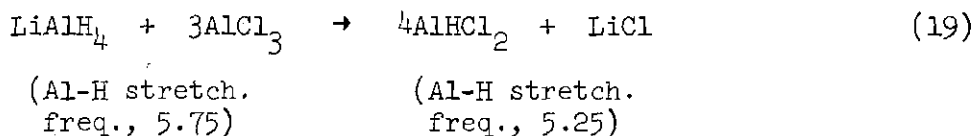
The compounds were isolated and characterized as diethyl etherates, triethylamminates and bis-triethylamminates. All of the above species were shown to be monomeric in diethyl ether. Evans¹⁸ and his co-workers followed the titration of ethereal aluminum chloride with lithium aluminum hydride conductimetrically, and rationalized their results by postulating the following stepwise reactions:



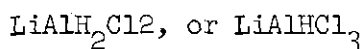
Ashby and Prather¹⁵ studied the reaction of lithium aluminum hydride and aluminum chloride, bromide, and iodide. They followed the progress of the reaction by infrared and elemental analysis of the

18. G. G. Evans, J. K. Kennedy, Jr., F. D. Del Greco, J. Inorg. Nucl. Chem., 4, 40 (1957).

reaction products. Their results could not be reconciled with Evans' postulates. They proposed the following stepwise reactions:

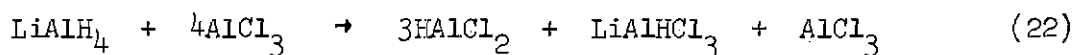


Lithium chloride would be expected to precipitate in all cases above, since it is insoluble in diethyl ether. However when lithium aluminum hydride and aluminum chloride are combined in molar ratios of one to one, or one to three, no lithium chloride precipitate is obtained.¹⁵ This was explained by postulating the existence of weak complexes between lithium chloride and the hydridoaluminum chlorides of the following type:



Attempts to confirm this by infrared or nuclear magnetic resonance spectral evidence were unsuccessful.

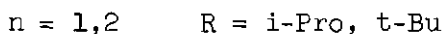
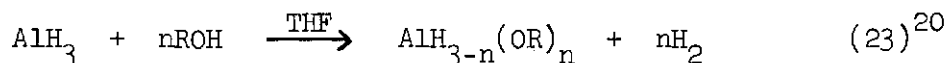
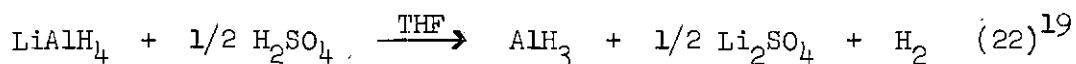
The evidence presented in the preceding paragraph strongly indicates that the reducing agent involved in the mixed hydride reductions discussed above is either some free hydridoaluminum halide, or some lithium chloride-hydridoaluminum halide complex. Furthermore, the three to one lithium aluminum hydride to aluminum chloride combination involves the formation of aluminum hydride, the one to one combination contains dihydridoaluminum chloride with some lithium chloride, and the one to four combination contains hydridoaluminum dichloride with lithium chloride and some excess aluminum chloride.¹⁵



These trivalent aluminum compounds would be expected to exhibit considerable Lewis acid character as well as fairly strong reducing properties. The electron withdrawing or donating power of the various substituent groups or solvating species might be expected to have a pronounced effect on these properties. Introduction of a more strongly electron withdrawing group (such as halogen) in aluminum hydride would enhance its Lewis acidity and diminish its reducing power. Complexation of the hydride species by basic solvating agents should have the opposite effect.

One of the goals of this work is the determination of the active species in the one to four reagent ($\text{LiAlH}_4:4\text{AlCl}_3$), i.e., does the excess aluminum chloride and complexed lithium chloride have any effect on the type of reactivity exhibited by this reagent? Other objectives include the determination of the effect of varying (1) the number of attached halogens (from none in aluminum hydride to two in hydrido-

aluminum chloride; (2) the halide itself from chlorine to bromine to iodine; (3) the basicity of the solvating species from diethyl ether to tetrahydrofuran to triethylamine; (4) the substituents themselves from halides to various alkoxy groups. An alkoxyaluminum hydride can be aluminum hydride as shown in the following equations:



The t-butoxyaluminum hydrides are dimeric in tetrahydrofuran, and exhibit bridging through the alkoxy groups. The isopropoxyaluminum hydrides as yet have not been studied.

Interesting interplays between steric and electronic effects would be expected to show up in these studies. A good system for studying all of these aforementioned effects would be some carefully chosen epoxide, as the following discussion will illustrate.

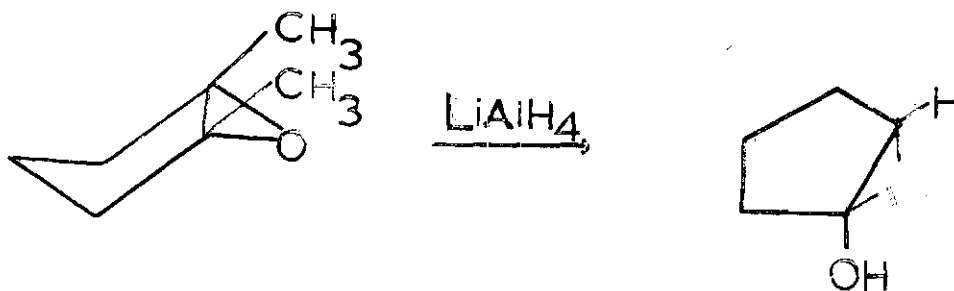
When epoxides are treated with lithium aluminum hydride, an $\text{S}_{\text{N}}2$ mechanism is operative²¹. This is shown by the fact that the sole

19. H. C. Brown and Nung Min Yoon, J. Am. Chem. Soc., 88, 1464 (1965).

20. H. Suchy, "Über Alan, Aluminiumboronate Und Tris(N-N-dimethylhydrazino)-boran" Dissertation, University of Munich, Munich, Germany 1966.

21. L. W. Trevoy and W. G. Brown, J. Am. Chem. Soc., 71, 1675 (1949).

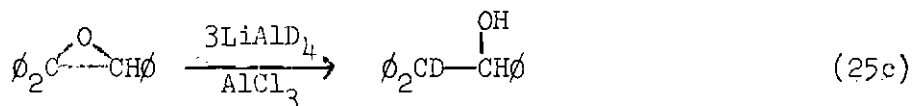
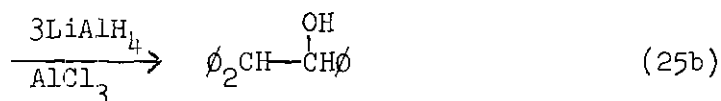
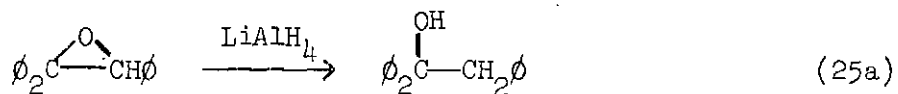
product isolated from the lithium aluminum hydride reduction of 1,2-dimethyl-1,2-epoxycyclopentane is trans-1,2-dimethylcyclopentanol,²¹ indicating that a Walden inversion has occurred.



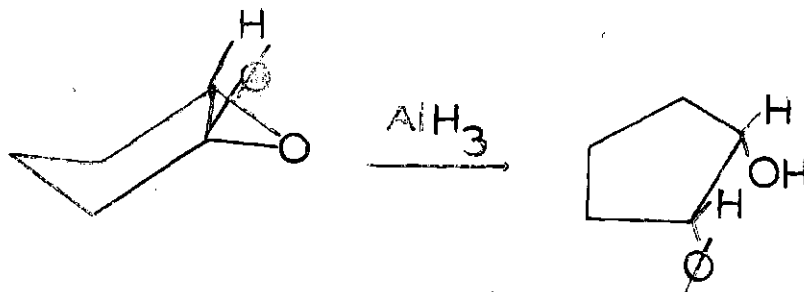
Also, the alcohol formed by lithium aluminum hydride reduction of epoxides is usually the most sterically hindered²¹, indicating attack of hydride donor at the least hindered site. This is also in agreement with an S_N2 mechanism.

When a weakly acidic mixed hydride, such as aluminum hydride, is treated with an epoxide, the reaction takes a different course. Products arising from attack at the most stable carbonium ion that could arise from cleavage of the oxirane ring prevail (eq. 25)²². Deuterium labeling experiments¹¹ have been shown that this reaction involves a direct reduction (eq. 26c). Stereochemical studies have shown¹⁶ that the reaction of epoxides with aluminum hydride involves

22. M. N. Rerick and E. L. Eliel, ibid., 84, 2356 (1962).



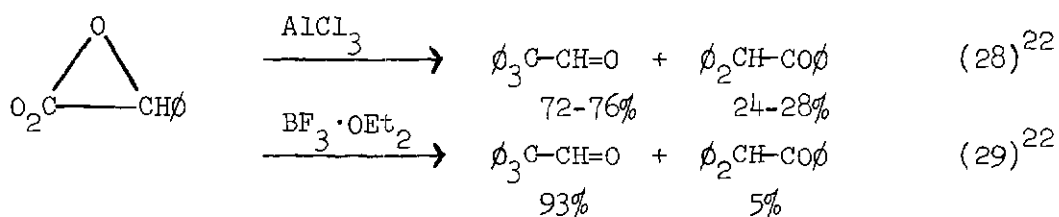
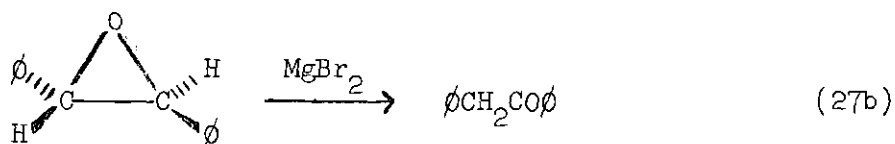
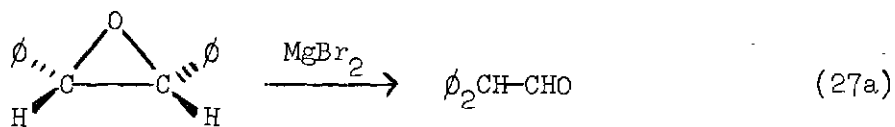
a backside donation of hydride by the reducing species.



It seems probable that Lewis acid catalysis is also involved in this reaction.

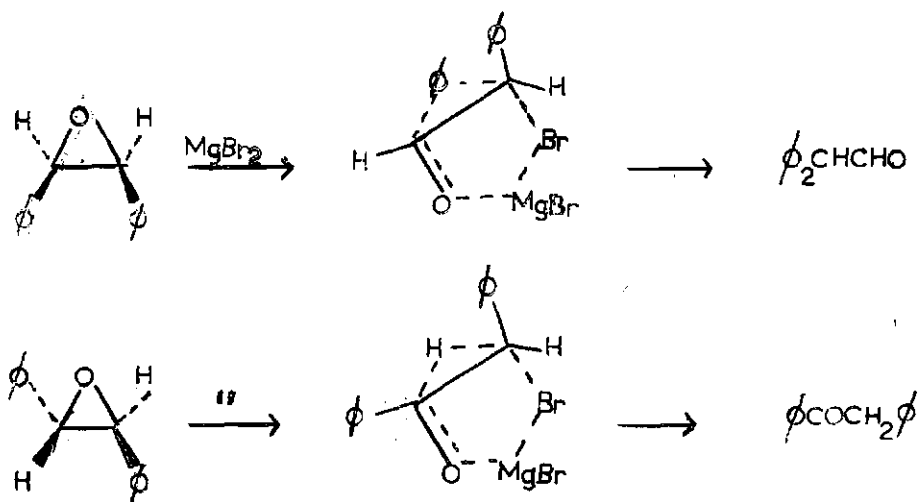
In the presence of stronger Lewis acids, epoxides can undergo ring opening and extensive rearrangements of their carbon skeletons^{20,21,23}.

23. H. O. House, *ibid.*, 77, 3070 (1955).

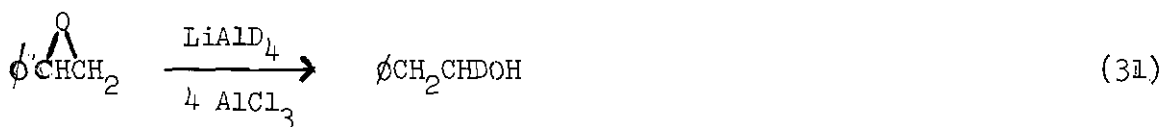
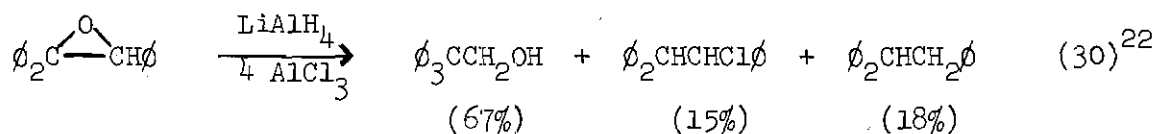


The reactions with magnesium bromide are thought to involve an intermediate complex with an O-Mg-Br bridge, as shown in figure 1 below. The boron trifluoride catalyzed rearrangement is thought to go through an intermediate in which the oxirane ring is largely cleaved, and which probably has considerable carbonium ion character²². The aluminum chloride catalyzed rearrangement of triphenylethylene oxide is thought to proceed by a route that is a combination of these two pathways²².

Figure I. The Magnesium Bromide Catalyzed Rearrangement of cis- and trans-Stillbene Oxide



That extensive rearrangements can take place when a strongly acidic mixed hydride is used as a reducing agent is illustrated by the following:

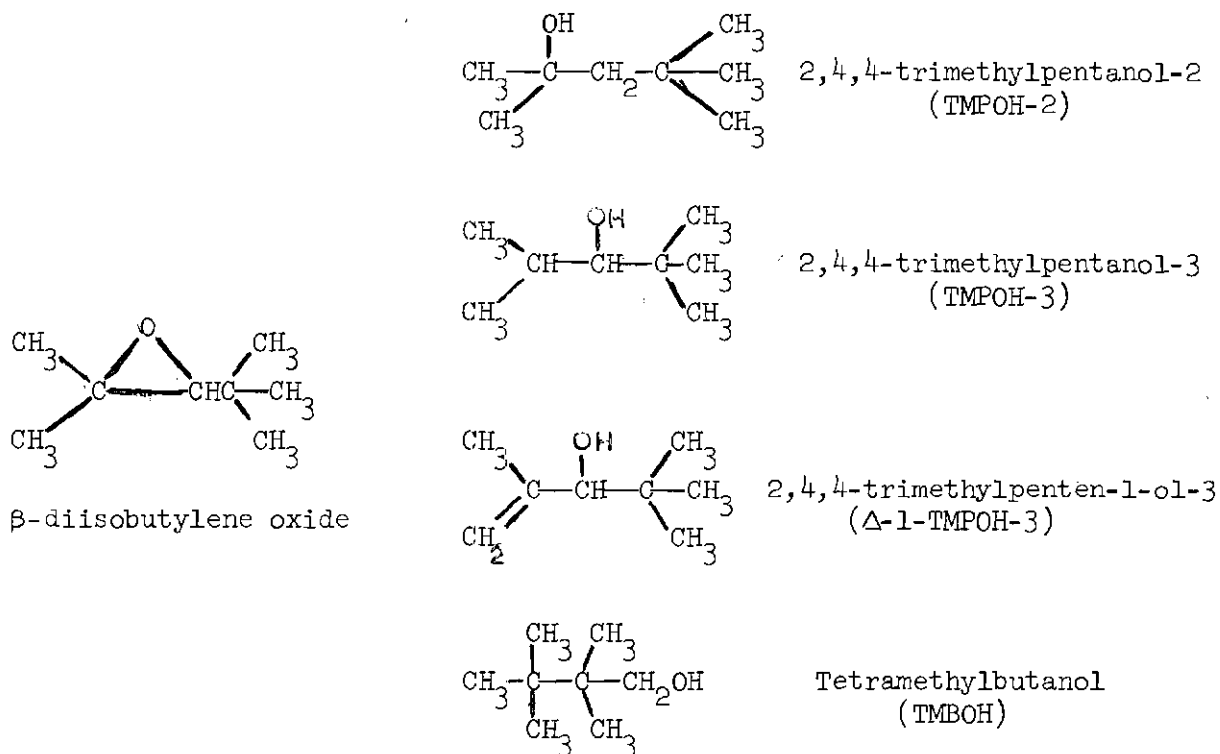


In (30) above, the major product, 2,2,2-triphenylethanol, is clearly the result of a phenyl shift, and in (31) above, the 2-phenylethanol-1-d arises from a hydride shift, and subsequent reduction of the resulting

aldehydic intermediate¹².

Our requirement for this study is an epoxide whose mixed hydride reduction products are separable by vapor phase chromatography, and are such that it is clear whether they arise from direct reduction, or from migration and subsequent reduction without making extensive use of deuterium labelling experiments. Some initial work was done on styrene oxide and triphenylethylene oxide, but these did not satisfactorily meet these requirements. However, past workers^{22,24} have shown that β -diisobutylene oxide should yield meaningful results in our study. When this epoxide is treated with various mixed hydride reagents, four products are formed whose ratios are strongly dependent on the type of reagent used. This is illustrated in Figure 2 and table 2 below:

24. L. I. Zakharkin, I. M. Khorlina, Izv. Akad. Nauk. S.S.S.R., Ser. Khim., 1965, 862.

Figure 2. β -diisobutylene Oxide and its Reduction ProductsTable 2. Products of Various Mixed Hydride Reductions
on β -diisobutylene Oxide²⁴

Mixed Hydride ^a Reagent	TMPOH-2 ^b	TMPOH-3	-1-TMPOH-3	TMBOH	Gross ^c Product Yield
LAH alone ^d	100	-	-	-	21%
3:1 LAH: AlCl ₃	36	50	10	4	96%
1:1 LAH: AlCl ₃	14	32	9	45	95%
1:4 LAH: AlCl ₃	-	15	8	77	83%

^a a three-fold excess of hydride over epoxide was used^b numbers in these columns are product ratios^c represents a material balance^d LAH means LiAlH₄

The initial undertaking of this project was to check these results. Then the work outlined briefly on page eight was done using the results of the check as a reference point. The results of these experiments and our interpretation of the data are given below.

CHAPTER II

EQUIPMENT, CHEMICALS AND PURIFICATION PROCEDURES

An F and M model 720 Dual Column Programmed Temperature Gas Chromatograph was used for all gas chromatography work. Nuclear magnetic resonance spectra were obtained using a Varian A-60 Nuclear Magnetic Resonance Spectrometer. A Perkin-Elmer 237-B Grating Infrared Spectrophotometer was used to obtain infrared spectra. Potentiometric titrations were done using a Beckman Zeromatic pH Meter.

All work involving the use of complex metal hydrides, aluminum halides, or Grignard reagents was done under a dry nitrogen atmosphere in heat-dried, nitrogen-purged glassware. Two types of procedures were used to furnish a dry nitrogen atmosphere:

(1) The system was connected directly to a nitrogen tank and closed to the atmosphere by means of a mercury bubbler partially filled with mineral oil. The systems were maintained under a slight positive pressure of nitrogen while they were in use.

(2) Other work done under a nitrogen atmosphere was carried out in a Kewaunee nitrogen box fitted with a recirculating system containing a Little Giant recirculating pump, an acetone-dry ice cooled trap for removing organic vapors, two columns packed with manganous oxide on vermiculite to remove residual oxygen, and a column packed with type 4A molecular sieves (1/16 inch in diameter) obtained from the Linde Company to remove residual water vapor.

The following materials were used in the preparation of the various hydride reagents: lithium aluminum hydride was obtained from Metal Hydrides, Inc. Ethereal lithium aluminum hydride solutions were prepared by overnight stirring of an ether-hydride slurry, filtration of undissolved material, and standardization of the resulting clear solution by the method outlined in chapter four. Anhydrous aluminum chloride and bromide (Certified Reagent) were obtained from the Fisher Scientific Company. Aluminum chloride was further purified by sublimation in vacuo. The aluminum bromide was used without further purification. Anhydrous aluminum iodide (Laboratory Chemical) was obtained from Fisher Scientific, and further purified by sublimation in vacuo. Ethereal aluminum halide solutions were standardized and used immediately after their preparation. Ethereal aluminum chloride solutions were prepared by addition of halide to ether at either minus 20 degrees centigrade or at room temperature. Mixed hydride reductions using both types of aluminum chloride solutions gave results identical within experimental error. Ethereal aluminum chloride solutions are stable at room temperature for at least 33 hours. This was shown by the fact that aluminum and chloride determinations done on aliquots periodically removed from an aluminum chloride solution yielded aluminum to chlorine ratios of one to three (within the experimental error expected for the analytical procedures). The stability of aluminum bromide and iodide solutions over a period of time was not determined. The aluminum iodide solution was prepared by addition of halide to ether cooled to minus ten degrees centigrade and allowing the resulting

solution to warm to room temperatures. The aluminum bromide solution was prepared by addition of halide to ether at minus ten degrees centigrade. The resulting solution was maintained at this temperature during its standardization and subsequent use. Fuming sulfuric acid (Reagent Chemical) was obtained from Fisher Scientific. Methanol and isopropanol were purified by distillation from magnesium turnings under a dry nitrogen atmosphere. Tertiary butanol was obtained from Fisher Scientific, and purified by distillation from potassium under a dry nitrogen atmosphere. The solvents listed below were purified by the following methods when they were used for hydride reactions or syntheses involving Grignard reagents. Anhydrous diethyl ether was obtained from Fisher Scientific and purified by distillation from lithium aluminum hydride through a packed column under a dry nitrogen atmosphere. Thiophene-free benzene, triethylamine and tetrahydrofuran, obtained from Fisher Scientific, Eastman Organic Chemicals, and Fisher Scientific respectively, were purified by distillation from sodium aluminum hydride through a packed column under a dry nitrogen atmosphere.

Other solvents used for synthetic work were the following: Carbon tetrachloride, obtained from the Columbia Southern Chemical Corporation, ligroin, obtained from Fisher Scientific, anhydrous pyridine, obtained from Baker Chemical Company and ethyl acetate, obtained from Fisher Scientific, were all used without further purification. Petroleum ether (B.P. 37.5-52.8) and hexane, obtained from Fisher Scientific and Matheson Chemical Companies respectively, were purified by successive washings with portions of dilute sulfuric acid, water, and bicarbonate solution. The olefin-free alkanes were then dried over anhydrous potassium carbonate.

The following starting materials were used for synthetic work: benzyl chloride and t-butyl chloride, obtained from Fisher Scientific, were purified by drying over anhydrous magnesium sulfate and distilling through a packed column under a dry nitrogen atmosphere. Magnesium turnings (Laboratory Chemical) were obtained from Fisher Scientific. Triply-sublimed magnesium was obtained from the Dow Chemical Company and machine-milled. The resulting turnings were washed with ether and dried. Benzophenone was obtained from Eastman Organic Chemicals and used without further purification. Crude isobutyraldehyde of unknown origin was purged with dry nitrogen for 15 or 20 minutes and used without further purification. Benzoyl peroxide and N-bromosuccinimide were obtained from Fisher Scientific and Eastman Organic Chemicals respectively and used without further purification. A sample of crude syn-7-norbornenol was kindly furnished by Mr. S. K. Gabriel. Purified 3,5-dinitrobenzoyl chloride was obtained from Fisher Scientific and used without further purification.

The following organic chemicals were used for mixed hydride reductions: styrene oxide was obtained from the Aldrich Chemical Company and was purified by drying over anhydrous potassium carbonate and by two distillations under reduced pressure through a packed column. This epoxide was stored under nitrogen, as were the other epoxides used in this study. Both 1- and 2-phenylethanol were also obtained from Aldrich, and were purified by distillation through a packed column under reduced pressure. The n-octanol used as an internal standard for chromatographic product analyses is of unknown origin and was purified by distillation through a packed column. Mr. S. K. Gabriel

furnished the exo-norbornene oxide used for the mixed hydride reductions. An authentic sample of endo-2-norbornanol was kindly furnished by Dr. E. L. Eliel. The β -diisobutylene oxide (from Union Carbide) was also furnished by Dr. Eliel, and was dried over anhydrous potassium carbonate and distilled twice through a spinning band column fitted with a sodium hydroxide-filled drying tube. A reflux ratio of 30 or 40 to one was used for these distillations. The distillate was deaerated by purging with dry nitrogen for 15 or 20 minutes. Vapor phase chromatographic analysis showed that the purified epoxide was only 97 percent pure. The boiling point (123-124°C) did not correlate well with the literature value²⁵ (130-131°C), but the results obtained from an NMR spectrum run on a sample of the neat liquid were consistent with those expected on the basis of the structure of β -diisobutylene oxide. Authentic samples of 2,4,4-trimethylpentanol-2 and tetramethylbutanol were kindly furnished by Dr. E. L. Eliel. An additional sample of tetramethylbutanol was isolated by preparative vapor phase chromatography from a mixture of the gross products from the reduction of β -diisobutylene oxide by the one to three and one to four lithium aluminum hydride to aluminum chloride reagents. The conditions used for the separation are the same as those used for the product analyses for this system. The physical properties of the white, crystalline solid were identical with those of the authentic tetramethylbutanol sample furnished by Dr. Eliel.

25. A. Byers and W. J. Hickinbottom, J. Chem. Soc., 1948, 284.

Other epoxides and reduction products studied in this work were prepared according to procedures outlined in chapter three.

CHAPTER III

SYNTHETIC WORK

A) 1,1,2-triphenylethanol: This compound was prepared by the method of Hell and Wiegant²⁶. Twenty-six grams (1.1 moles) of triply sublimed magnesium was put into a flame-dried two liter three-necked round-bottomed flask that had been purged with dry nitrogen, and fitted with a mechanical stirrer, acetone/dry ice condenser, and two addition funnels. One funnel contained 127 grams (1.0 mole, 115 ml.) of benzyl chloride, the other contained approximately one liter of distilled diethyl ether. Ether and halide were added concurrently at the rate of one or two drops a second. The resulting mixture was allowed to stir for three hours.

To about 400 milliliters of distilled ether was added 172 grams (1 mole) of benzophenone. This solution was added to the above Grignard solution over a period of one hour for an additional two hours. Then 250 milliliters of water followed by 250 milliliters of ten percent sulfuric acid were carefully added. The aqueous and ethereal layers were separated, and the aqueous layer was discarded. Ten grams of anhydrous sodium carbonate were added to the ether layer. After about 30 minutes the ether solution was decanted away from the carbonate. The ether was removed in vacuo, and the resulting white solid was recrystal-

26. C. Hell and F. Wiegant, Ber., 37, 1429 (1904).

lized from a mixture of four parts ligroin and one part benzene. This procedure produced 226 grams (0.886 moles, 87 percent yield) of white, crystalline material, M.P. = 87-89°C (lit. M.P. = 97-89°)²⁵.

A repeat of this procedure using magnesium turnings resulted in the isolation of 1,1,2-triphenylethanol in 81 percent yield.

B) Triphenylethylene Oxide:

1) 1,1,2-triphenyl-2-bromoethanol: The procedure of Lane and Walters²⁷ was used to make this compound and triphenylethylene oxide. Two hundred and twelve grams of 1,1,2-triphenylethanol (0.824 moles) and 170 grams of N-bromosuccinimide (0.955 moles) were dissolved in refluxing carbon tetrachloride. To this solution was added 0.5 grams of benzoyl peroxide. The resulting mixture was refluxed for three and one half hours, allowed to cool, and filtered to remove the insoluble succinimide. The carbon tetrachloride was removed in vacuo. A viscous, orange oil which had a pungent halogen-like odor resulted. This product was recrystallized twice from ligroin and dried in vacuo for two hours. This procedure resulted in the isolation of 66.3 grams (0.204 moles, 25 percent yield) of white, crystalline material, M.P. = 123-127°C. (lit. M.P. = 124-126°C).

A repeat of the above procedure, differing only in that the reaction mixture was refluxed for six hours, resulted in the isolation after one recrystallization of 1,1,2-triphenyl-2-bromoethanol in 80.5 percent yield, M.P. = 124-126°C.

27. J. F. Lane, D. R. Walters, J. Am. Chem. Soc., 73, 4234 (1951).

2) Triphenylethylene Oxide: To an ether solution containing 66.3 grams (0.204 moles) of 1,1,2-triphenyl-2-bromoethanol was added 20 grams of pulverized potassium hydroxide. The resulting slurry was stirred for 24 hours. The ether solution was decanted away from the solid precipitate, and was concentrated to dryness in vacuo. The resulting white solid was washed with water, and recrystallized from absolute methanol. The resulting crystalline material was dried in vacuo. This procedure resulted in the isolation of 32 grams (0.125 moles, 61 percent yield) of white, crystalline triphenylethylene oxide, M.P. = 75-77°)²⁷

A repeat of this reaction resulted in the isolation of pure triphenylethylene oxide in 81 percent yield.

C) 2,2,2-triphenylethanol: The procedure of Rerick and Eliel was used to make this compound²². A one to four LiAlH_4 to AlCl_3 reagent was prepared in the following manner: To 37.9 grams (284.2 millimoles) of anhydrous aluminum chloride in 500 milliliters of freshly distilled ether was added 25 milliliters of a 2.84 solution of lithium aluminum hydride (71.05 millimoles). The resulting solution was allowed to come to room temperature, and filtered in the nitrogen box and analyzed for aluminum. The results of this analysis are given below:

$$\begin{aligned} [\text{Al}]_{\text{tot}} &= 1.17\text{M} & [\text{AlHCl}_2] &= 4/5[\text{Al}]_{\text{tot}} = 0.934\text{ M} \\ [\text{AlCl}_3] &= 0.234\text{ M} \end{aligned}$$

To 23 milliliters of the above solution (20.4 millimoles) of AlHCl_2 was added an ether solution containing five grams (19.5 millimoles) of triphenylethylene oxide. The resulting solution was stirred for five and

one half hours. The reaction mixture was hydrolyzed with about 20 milliliters of water, followed by ten milliliters of ten percent hydrochloric acid solution. The ethereal and aqueous layers were separated, and the water layer was extracted with two small portions of ether. The ether layers were combined and dried over anhydrous potassium carbonate. The ether layer was decanted away from the carbonate, and concentrated to dryness in vacuo. A white semisolid resulted, which crystallized upon standing overnight. The material was recrystallized from ligroin and petroleum ether. This procedure resulted in the isolation of 1.3 grams of white, crystalline 2,2,2-triphenylethanol, M.P. = 103-105°C (lit. M.P. = 103-105°)²².

D) 1,2,2-Triphenylethanol: 11.7 milliliters (22.5 millimoles) of 1.93 M lithium aluminum hydride in ether was added to about 200 milliliters of distilled ether in a 500 milliliter three-necked round-bottomed flask fitted with a teflon stopcock, sintered glass filter, vacuum side-arm, and 24/40 standard taper male joint at the bottom. The joint was fitted with a three-necked round-bottomed flask fitted with a pressure equalizing dropping funnel. To the top flask containing the lithium aluminum hydride solution was added with stirring 8.0 grams (7.5 millimoles) of anhydrous aluminum chloride. After 30 minutes, the resulting aluminum hydride solution was filtered through the frit into the bottom flask under reduced pressure. An ethereal solution containing 4.0 grams of triphenylethylene oxide was added through the addition funnel to the flask containing the aluminum hydride solution. The resulting mixture was stirred for two hours at room temperature. Twenty-five milliliters of water followed by 35 milliliters of saturated sodium

bitartrate solution were then carefully added to the reaction mixture. The ethereal and aqueous layers were separated, and the aqueous layer was extracted with four 40 milliliter portions of ether. The ether layers were combined and dried over anhydrous potassium carbonate for about 30 minutes, and dried in vacuo. This resulted in the isolation of 3.75 grams of a greenish, viscous oil. The crude product was recrystallized twice from acid-washed hexane and once from acid-washed petroleum ether. The resulting crystals were dried in vacuo. The entire procedure resulted in the isolation of 1.58 grams (6.4 millimoles, 40 percent yield) of crude, crystalline 1,2,2-triphenylethanol, M.P. = 84-86.5°C (lit. M.P. - 87-89°)²². A vapor phase chromatography experiment using a two foot column packed with ten percent carbowax 20M on diatoport S at 220 degrees showed that the product was about 95 percent pure.

E) exo-2-norborneol: Ten grams (90.8 millimoles) of exo-norbornene oxide was added to a tetrahydrofuran solution containing 25 millimoles of lithium aluminum hydride. The resulting solution was refluxed under nitrogen atmosphere for one week. Five milliliters of ethyl acetate was added carefully to the cooled reaction mixture to destroy the unreacted lithium aluminum hydride. Then 50 milliliters of water, followed by 25 milliliters of ten percent sulfuric acid was added. The resulting mixture was extracted with five small portions of acid-washed petroleum ether. The organic layers were combined and dried over potassium carbonate, and the solvent was removed in vacuo. A white solid was obtained, which was sublimed at 75 degrees and 0.75 millimeters of

mercury. This resulted in the isolation of 6.7 grams (44 millimoles, 67 percent crude yield) of crude exo-2-norborneol, M.P. = 102-113°C (lit. M.P. = 124-125°C)²⁸. An attempted recrystallization of the product from ligroin, and a successful recrystallization from pet. ether resulted in the isolation of 2.35 grams (21.5 millimoles, 24 percent yield) of exo-2-norbornanol, M.P. = 123-125°C. The above procedure was first carried out by Hanack and Kaiser²⁸.

F) 7-norborneol: This compound was synthesized according to the method of Franzus and Snyder²⁹. To a 12 milliliter ethereal solution containing 8.5 millimoles of lithium aluminum hydride was added 0.307 grams (2.84 millimoles) of crude syn-norbornen-2-ol-7. The resulting mixture was stirred for 12 hours. About 80 percent of the reaction mixture was spilled during workup. The remainder was hydrolyzed with water and saturated bitartrate solution. The ethereal and aqueous layers were separated, and the aqueous layer was extracted with two small portions of ether. The combined ether layers were dried over potassium carbonate, and concentrated to dryness in vacuo. Twenty milligrams of crude product resulted, M.P. = 130-140°C (lit. M.P. = 150-151°)²⁹. Vapor phase chromatography done on a six foot column packed with Ucon Polar oil on diatoport S showed that the product was about 90-95 percent pure. An NMR spectra of a carbon tetrachloride solution of the product showed the following absorbtions. Tetramethylsilane

28. M. Hanack and W. Kaiser, Ann. 657, 12 (1962).

29. B. Franzus, E. I. Snyder, J. Am. Chem. Soc., 87, 3423 (1965).

was used as an external standard. The absence of a signal at 4.3 to 4.7 τ shows that the carbon-carbon double bond has indeed been reduced. Since lithium aluminum hydride is not known to catalyze skeletal rearrangements, we can regard the structure of the product to be proved as assigned.

position of absorbtion	assignment
6.08 τ (singlet)	CH-O
7.35 τ (singlet)	OH
8.08 τ (singlet)	ring protons
8.30 τ (singlet)	ring protons
8.78 τ (singlet)	ring protons
8.97 τ (singlet)	ring protons

G) 2,4,4-trimethylpentanol: An ether solution containing 13.9 grams (0.15 moles) of dry, distilled, oxygen-free t-butyl chloride was added over a 40 minute period to 3.8 grams (0.17 moles) of magnesium turnings. The resulting mixture was stirred for an additional 20 minutes. To this was slowly added an ether solution containing 8.83 grams (0.115 moles) of isobutyraldehyde. The reaction mixture was stirred for 20 minutes, and was hydrolyzed with water, followed by ten percent hydrochloric acid solution. The ethereal and aqueous layers were separated, and the aqueous layer was discarded. The ether layer was washed with three small portions of sodium bicarbonate solution, and dried over potassium carbonate. The gross product was concentrated to

dryness in vacuo. This procedure resulted in the isolation of 5.3 grams of a yellow liquid. Analysis using V.P.C. showed that this liquid consisted of about 65 mole percent of the desired product. An attempt was made to fractionally distill the product in Bantamware. Four fractions were obtained (lit. B.P. = 155°C)³⁰.

fraction no.	boiling pt. range	approx. vol. (ml.)
1	43-75°	2.5
2	85-95°	0.4
3	148-151°	1.5
4	pot residue	4-5

Pure 2,4,4-trimethylpentanol was isolated from the third fraction by preparative vapor phase chromatography. A six foot column packed with ten percent Apiezon L on Diatoport S was used for the separation. The conditions are listed below:

column temp. = 125° det. temp. = 350°
inj. port temp. = 250° bridge current = 150 mA
He flow = 30 cc/min. column diameter = $1/4$ in.
retention time of product = 5 min.

30. E. A. Cadwallader, A. Fookson, J. Research Nat. Bureau Standards, 41, 111 (1948).

H) 2,4,4-trimethylpenten-1-ol-3: This compound was prepared according to the procedure of Rerick and Eliel²². The procedure involves two steps, which will be outlined below.

1) 3,5-dinitrobenzoate of 2,4,4-trimethylpenten-1-ol-3: To 12 grams (0.0984 moles) of 96 percent pure β -diisobutylene oxide in 100 milliliters of dry pyridine was added 25 grams (0.108 moles) of 3,5-dinitrobenzoyl chloride. The resulting mixture was refluxed for four hours in a 200 ml round-bottomed flask fitted with a water-cooled condenser with a calcium chloride-filled drying tube. The reaction mixture was allowed to cool and poured into about 700 milliliters of ten percent hydrochloric acid and ice. A brown solid resulted, which was filtered out and washed with small portions of water, dilute alkali, and water. The crude product was allowed to dry overnight and recrystallized from a mixture consisting of nine parts hexane and one part ethyl acetate. This resulted in the isolation of 16.3 grams (0.051 moles, 52 percent yield) of crude material, M.P. = 111-117° (lit. M.P. = 120°)²².

2) 2,4,4-trimethylpenten-1-ol-3: To 200 milliliters of methanol was added 13.2 grams (0.046 moles) of the crude product from above. To this was added 200 milliliters of 20 percent aqueous sodium hydroxide. An exothermic reaction took place and the solution turned dark red. The solution was refluxed for three and one half hours, and allowed to cool. The cooled reaction mixture was extracted with four 50 milliliter portions of ether. The ether layers were combined and washed with two 100 milliliter portions of water, and then dried for six hours over potassium carbonate. The ether solution was concentrated to dryness in vacuo. This resulted in the isolation of 4.8 grams

(100 percent crude yield) of a yellow-brown liquid. Analysis of the crude product by vapor phase chromatography showed several minor components and one major component comprising about 86 mole percent of the mixture. This component was collected by preparative VPC, from a six foot column packed with ten percent Carbowax 20M on Diatoport S, under the following conditions:

col. tem = 135°C	He flow = 30 cc/min.
inj. port. temp. = 250°C	bridge current = 150 mA
det. temp. = 350°C	col. diameter = 1/4 in.
retention time of main product = 10.4 min.	

This procedure resulted in the isolation of 2.69 grams (0.0257 moles, 56 percent yield) of a clear liquid. This liquid was shown to be 2,4,4-trimethylpenten-1-ol-3 by the following NMR data. Assignments were made on the basis of the integration heights and on known literature correlations³¹. Tetramethylsilane was used as an external standard. The solvent was carbon tetrachloride.

position of absorbtion	no. of protons	assignment
5.36 τ (singlet)	2	H ₂ C=
6.47 τ (singlet)	1	CH-O
6.90 τ (singlet)	1	O-H
8.50 τ (singlet)	3	CH ₃ -C=
4.39 τ (singlet)	9	CH ₃ C

31. J. R. Dyer, Applications of Absorbtion Spectroscopy of Organic Compounds, Prentice-Hall, Inc. Englewood Cliffs, N.J., 1965.

CHAPTER IV

ANALYTICAL PROCEDURES

A) Inorganic Reagents:

1) Sampling Procedures: Aliquots of ethereal lithium aluminum hydride solutions were transferred to volumetric flasks, and hydrolyzed with isopropanol. Aliquits of aluminum halide solutions were transferred to volumetric flasks containing isopropanol and a few sodium hydroxide pellets; both types of samples were then acidified with dilute nitric, or sulfuric acid to dissolve any basic aluminum salts not in solution. Enough distilled water was then added to the samples in the flasks to bring the solution level up to the mark.

2) Aluminum Analyses: Aliquots of the samples prepared as above were transferred to Erlenmeyer flasks and made basic to methyl red with ammonium hydroxide solution. A measured excess of standardized EDTA (ethylenediaminetetraacetic acid) solution was added and the resulting solution was boiled for about three to five minutes. The samples were allowed to cool to room temperature or below. The samples were then buffered to a pH of about four. A volume of ethanol approximately equal to the volume of the cooled solution, along with a small amount of dithizone indicator in ethanol was then added. The excess EDTA was then titrated with a standard zinc sulfate solution to a blue-green to red color change. The amount of aluminum in the aliquot can be calculated from the following equation:

$$\text{mmoles Al} = \text{ml. EDTA} \times N_{\text{EDTA}} - \text{ml. ZnSO}_4 \times N_{\text{ZnSO}_4} \quad (32)$$

3) Halide Analyses: Chloride analyses were performed potentiometrically, and bromides and iodides were determined by the Volhard method. Both methods will be discussed in more detail below:

a) Potentiometric Halide Determinations: An aliquot of the prepared sample was transferred to a beaker, diluted to about 50 to 75 milliliters total volume, and acidified to a pH of about three with dilute nitric acid. Five milliliters of ethanol were then added to render the resulting silver chloride precipitate more insoluble. The solution was then titrated with standard silver nitrate solution. The titration was followed potentiometrically, using a pH meter. The reading on the pH scale should be about three at the beginning of the titration. A pH reading of 4.3 to 4.5 corresponds to the endpoint.

b) Volhard Determinations: An aliquot of the prepared sample was diluted with distilled water and acidified with five percent sulfuric acid. Ferric alum indicator was then added, along with about ten milliliters of benzyl alcohol per 100 milliliters of solution. A measured excess of standard silver nitrate solution was added with vigorous swirling. The excess silver nitrate solution was titrated with standard potassium thiocyanate solution until the appearance of a reddish-brown color. The amount of halide in the aliquot of prepared sample is calculated from the following equation:

$$\text{mmoles halide} = \text{ml. AgNO}_3 \times N_{\text{AgNO}_3} - \text{ml. KCNS} \times N_{\text{KCNS}} \quad (33)$$

B) Product Ratios from Mixed Hydride Reductions: The products from mixed hydride reductions were identified by comparison of retention times under a standard set of conditions with those of authentic samples. Quantitative analyses of products were accomplished by comparison of peak areas due to the products with the peak area due to a carefully measured amount of an internal standard. The peak areas were determined by using a planimeter. The following derivation will illustrate the principles involved:

The area under some peak due to a compound, a, is directly proportional to the amount of compound a present, i.e.,

$$A_a = k_a \text{ wt.}_a \quad (34)$$

$$\begin{array}{ll} A_a = \text{area due to a} & k_a = \text{proportionality constant} \\ \text{wt.}_a = \text{weight of a in sample} & \end{array}$$

The same relationship holds true for any compound, b, i.e.,

$$A_b = k_b \text{ wt.}_b \quad (35)$$

Division of eq. (35) by eq. (34), and rearrangement yields the following relationship:

$$\frac{k_b}{k_a} = \frac{\text{wt.}_a \times A_b}{\text{wt.}_b \times A_a} = Z_{(b/a)} \quad (36)$$

Let b be the internal standard, and a be the product to be determined. The constant, $Z_{(b/a)}$, can be determined by weighing known amounts of b and a, injecting the mixture into the VPC, determining the peak areas, and substituting the appropriate values for the weights and areas into equation (36). Rearrangement of equation (36) yields the following relationship:

$$\text{wt.}_a = Z_{(b/a)} \frac{A_a \times \text{wt.}_b}{A_b} \quad (37)$$

If a known amount of internal standard is weighed into the gross product of a mixed hydride reduction, and a sample of the resulting mixture is injected into the VPC, and the areas of the peaks due to a and the standard b are determined, then the weight of product a present can be determined by substitution of the appropriate values in equation (37). The advantage of this method is that it is not a volumetric method, and its success depends only on the determination of the weight of the standard, and the areas due to the product and standard.

During the course of this work the reactions of several substrates with various mixed hydrides were studied. Chromatographic data on the starting materials and products will now be presented:

1) Styrene Oxide and its Products: When styrene oxide is treated with a mixed hydride reagent, 1- and 2-phenylethanol are obtained in varying relative amounts depending on the properties of the mixed hydride used.¹² These products can be determined chromatographically by using a six foot column packed with 20 percent Carbowax 20M

on Chromosorb P. The internal standard used was n-octanol. Values for Z were determined from chromatograms of carefully weighed samples of the above compounds and the standard by the method outlined above. The data obtained is shown in table III, below:

Table 3. Vapor Phase Chromatography Data on
Styrene Oxide and Its Reduction Products

compound	retention time (mins.)	Z (oct. compd)
$\text{C}_6\text{H}_5\text{CH} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{CH}_2 \end{array}$ (styrene oxide)	9.4	1.22
$\text{C}_6\text{H}_5\text{CHOHCH}_3$ (1-phenylethanol)	13.8	1.12
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{OH}$ (2-phenylethanol)	18.3	1.22
n-octanol	5.8	-

col. temp. = 185°C

det temp - 350°C

inj. port temp = 250°C

H_e flow - 30 cc/min.

bridge current - 150 mA

column diameter = 1/4 in.

2) Triphenylethylene Oxide and its Products: When triphenylethylene oxide is treated with various mixed hydride reagents, several products can be formed, which depend on the properties of the mixed hydride. Among these are 1,1,2-, 1,2,2-, and 2,2,2-triphenylethanol²². Numerous attempts were made to separate these products, using vapor phase chromatography. Several columns were tried under widely varying conditions. None of these experiments was successful. The columns and conditions tried are listed in Table 4.

Table 4. Chromatography Conditions Used in Attempts to Separate 1,1,2-, 1,2,2-, and 2,2,2-triphenylethanol.

column packing	length (ft.)	col. temp. (°C)	He flow (ccs/min.)
10% SE 30*	2	185-250	200-250
10% SE 30	6	185-250	200-250
10% Apiezon L	6	200-240	150
10% Carbowax 20M	2	200-240	150
10% Carbowax 20M	3	200-240	150

*all column diameters are 1/4 in.

3) exo-Norbornene Oxide and its Reduction Products: Vapor phase chromatography experiments on products of mixed hydride reductions of this epoxide were performed by Mr. Sammy K. Gabriel on an F and M model 400 Biomedical gas chromatograph. A six foot column packed with

two to three percent Ucon Polar on Chromosorb Q was used. Four components, listed as (a) through (d) in Table 5, appear in the gross products of all mixed hydride reductions performed on this epoxide. Not all of these components have been identified yet, and the product ratios have not been calculated.

Table 5. Vapor Phase Chromatography Data on exo-Norbornene Oxide and its Reduction Products.

component	known compounds	retention times (mins)
-	exo-norbornene oxide	0.90
(a)	-	2.18
-	<u>exo</u> -2-norborneol	2.10
(b)	-	2.30
-	<u>endo</u> -2-norborneol	2.30
-	7-norborneol	2.28
(c)	-	3.35
(d)	-	7.50

col. temp. = 100°C

det. temp. = 180°

inj. port temp. = 190°C

H_e flow = 56 cc/min.

col. diameter = 1/4 in.

4) β -diisobutylene Oxide and its Products: The products of mixed hydride reductions performed on this epoxide are listed in figure 2 on page 13, as are the abbreviations which will be used here. The product ratios were determined from data obtained using a six foot column packed with ten percent Carbowax 20M on Diatoport S. The internal standard used was n-octanol. Values for Z were determined from chromatograms of carefully weighed samples of each of the products and the standard by the method outlined above. Two of the products, 2,4,4-trimethylpentanol-2, and 2,4,4-trimethylpentanol-3 were not separated cleanly by this procedure, but the separation obtained was good enough that the accuracy of the product ratios was not adversely affected. Chromatography data on these compounds is presented in Table 6.

The Z values shown in Table 6 indicate that, except for the olefinic alcohol (Δ -1-TMPOH-3), the areas under the peaks due to the products are directly proportional in the same manner to the mole percentages of the products. The area due to the olefinic alcohol can be corrected so that it is proportional to the mole percentage in the same manner as those for the other products. The total material balance can be obtained by comparing the total area under all peaks due to products with the same area under the peak due to the internal standard n-octanol. This procedure was used to calculate all product ratios and material balances from mixed hydride reductions of β -diisobutylene oxide, and will be illustrated by a set of sample calculations in the appendix.

Table 6. Vapor Phase Chromatography Data on β -diisobutylene Oxide and its Reduction Products.

compound	retention time (min.)	Z (oct./cmpd.)
epox.	2.2	1.01
TMPOH-2	5.6	1.02
TMPOH-3	6.8	1.01
Δ -1-TMPOH-3	9.0	1.08
TMBOH	12.8	1.01
n-octanol	18.0	-

col. temp. = 135°C

det. temp. = 350°C

inj. port temp. - 250°C

H_e flow = 40 cc/min

bridge current - 150 mA

column diameter = 1/4 in.

CHAPTER V

MIXED HYDRIDE REDUCTIONS

A) Styrene Oxide: The following procedures were used for all mixed hydride reductions carried out on this epoxide. The mixed hydride reagents were prepared in the following manner: Freshly distilled ether was added to a three-necked round-bottomed flask fitted with a mechanical stirrer, an addition funnel with a pressure equalizing sidearm, and a dry ice/acetone cooled condenser. The ether was cooled in a dry ice/acetone bath and a carefully weighed amount of anhydrous aluminum chloride was added. A measured amount of lithium aluminum hydride was then added dropwise to the cooled aluminum chloride-ether slurry. The resulting mixture was allowed to warm to room temperature and transferred to the nitrogen box where it was filtered through a sintered glass filter. An aliquot was taken and an aluminum analysis run.

A measured amount of an ethereal styrene oxide solution of known concentration was added to a measured amount of standardized mixed hydride solution and an amount of ether sufficient to make the reaction mixture up to a certain standard volume. The resulting mixtures were allowed to stand for two hours and worked up in the following manner:

Ten milliliters of water and ten milliliters of saturated sodium bitartrate solution were carefully added to the reaction mixture. The ethereal and aqueous layers were separated and the aqueous layer was extracted with three ten milliliter portions of ether. The ether layers

were combined and dried over anhydrous sodium carbonate. A weighed amount of n-octanol, the internal standard for chromatographic product ratio determinations, was added and the solution was concentrated to about one tenth of its original volume. The product ratios were then determined. The following reductions were carried out on styrene oxide in this manner:

1) Lithium Aluminum Hydride Alone: To 50 milliliters of distilled ether was added 1.23 milliliters of (3.49 millimoles, 14 milliequivalents hydride) of 2.84 molar lithium aluminum hydride and ten milliliters (14.3 millimoles) of 1.43 molar ethereal styrene oxide. An exothermic reaction took place. The ether refluxed in the reaction flask for two or three minutes. The reaction and workup procedures listed above were followed except that the aqueous layer was acidified with dilute mineral acid to dissolve the basic aluminum salts 0.566 grams of n-octanol was added, and the concentrated reaction mixture was chromatographed to determine the product ratios (entry no. 1, Table 7).

An identical reduction was performed, except that 1.51 milliliters (4.28 millimoles, 17.2 milliequivalents hydride) of 2.84 molar lithium aluminum hydride was used, and 0.845 grams of n-octanol was added (entry no. 2, Table 7).

2) One to Three LiAlH_4 to AlCl_3 Reagent: The mixed hydride reagent was prepared by mixing 32.7 grams (0.213 moles) of aluminum chloride and 25 milliliters (0.071 moles, 0.284 equivalents hydride) of 2.84 molar lithium aluminum hydride and 800 to 900 milliliters of distilled ether. An aluminum analysis showed the following results:

$$[Al]_{tot} = [HAlCl_2] = 2.25M$$

To 2.67 milliliters (6.01 mmoles $HAlCl_2$) of the above reagent was added ten milliliters of distilled ether and 50 milliliters (6.01 mmoles) of 0.1201 molar styrene oxide solution. An exothermic reaction occurred. 0.642 grams of n-octanol was added after hydrolysis to the gross product and the product ratios and material balances were determined (Entry 5, Table 7).

An identical reduction was performed except that 3.20 milliliters (7.2 millimoles $HAlCl_2$) of the mixed hydride reagent was used and 0.489 grams of n-octanol was added (Entry 4, Table 7).

3) One to Four $LiAlH_4$ to $AlCl_3$ Reagent. The mixed hydride reagents was prepared from 37.9 grams (0.284 moles) of aluminum chloride, 500 milliliters of ether and 25 milliliters (0.071 moles) of 2.84 molar lithium aluminum hydride solution. An aluminum analysis showed the following results.

$$[Al]_{tot} = 1.17M \quad [HAlCl_2] = 4/5[Al]_{tot} - 0.934M$$

$$[AlCl_3] = 0.234M$$

To a solution containing 40 milliliters of ether and 7.66 milliliters (7.15 millimoles $HAlCl_2$) of the above reagents was added 5 milliliters (7.15 mmoles) of 1.43 molar styrene oxide solution. An exothermic reaction occurred. 0.797 grams of n-octanol were added during the workup, and the product ratios were determined. (Entry no. 4, Table 7).

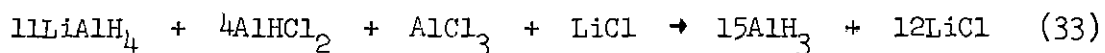
B) exo-Norbornene Oxide: The same type of procedure was used for

reactions performed on this epoxide as was used for styrene oxide reductions except that a reaction time of 47 hours was used, and the reaction mixtures were thermostatted at 25 degrees in a constant temperature bath. Enough ether was added to the hydride reagent so that the total volume of the reaction mixtures was 25 milliliters. The following reductions were performed in this manner:

1) Lithium Aluminum Hydride Alone: To 0.35 milliliters (1.0 mmoles, 3.98 mequivalents hydride) of 2.84 molar lithium aluminum hydride solution and 13.6 milliliters of ether was added 10 milliliters (3.98 millimoles) of 0.398 molar exo-norbornene oxide in ether. The reaction mixture was worked up in the usual manner and given to Mr. S. K. Gabriel for analysis.

2) One to Four LiAlH_4 to AlCl_3 Reagent: To 4.6 milliliters (3.98 mmoles HAlCl_2) of the one to four reagent used in the styrene oxide reduction, and 10.4 milliliters of ether was added 10 milliliters (3.98 mmoles) of the above epoxide solution. The reaction mixture was worked up in the usual manner and given to Mr. S. K. Gabriel for analysis.

3) Three to One LiAlH_4 to AlCl_3 Reagent (With ten percent Excess LiAlH_4): A solution of three to one reagent was prepared from the one to four reagent and the lithium aluminum hydride solution according to the following equation:



A ten percent excess of lithium aluminum hydrides was added to stabilize the resultant aluminum hydride.

To 0.38 milliliters (1.07 mmoles) of 2.84 molar lithium aluminum hydride solution plus 13.5 milliliters of ether was added 1.13 milliliters of the one to four reagent (1.06 mmoles HAlCl_2 and 0.265 mmoles AlCl_3) used above (this mixture consists of 1.66 mmoles AlH_3 and 0.166 mmoles LiAlH_4). To this reagent was added 10 milliliters (3.98 meq) of exo-norbornene oxide solution. The reaction, workup and product determination were carried out as usual.

4) Three to One LiAlH_4 to AlCl_3 Reagent: This reagent was prepared in the same manner as that used in the synthesis of 1,2,2-triphenylethylene oxide. To 25 ml of ether was added 0.275 grams (2.06 mmoles) of anhydrous aluminum chloride. To this was added 3.2 milliliters of 1.93 molar (6.2 mmoles) ethereal lithium aluminum hydride solution. To the filtered reagent was added 0.80 grams (8.24 mmoles) of exo-norbornene oxide in 20 milliliters of ether. The rest of the reaction, workup, and product determination were carried out in the usual manner.

C) β -Diisobutylene Oxide: Mixed hydride reagents were prepared in the nitrogen box by slowly adding measured amounts of freshly standardized lithium aluminum hydride solution to a flask containing a magnetic stirrer, a measured amount of a freshly prepared and standardized ethereal aluminum chloride solution, and an amount of ether sufficient to bring the resulting reaction mixture up to a certain approximate volume. Any solid material which appeared was not removed. The reagent was allowed to stand for from 20 to 30 minutes, and then a measured amount of standard β -diisobutylene oxide (usually 0.500 grams, 3.9 mmoles). The ether refluxed, indicating that an exothermic

reaction was occurring. The resulting mixture was allowed to stand for two hours and then was carefully hydrolyzed with 10 milliliters of water and enough dilute mineral acid to dissolve any basic aluminum salts. The ethereal and aqueous layers were separated and the aqueous layer extracted with three five milliliter portions of ether. The ether layers were combined and dried over anhydrous potassium carbonate. A measured amount (usually from a standard ether solution) of n-octanol was added to the dried product solution, and the resulting solution was concentrated to about one tenth of its original volume in vacuo. The product ratios were determined chromatographically. The following reactions were carried out on β -diisobutylene oxide in this manner, and duplicate runs were made, unless otherwise stated:

1) LiAlH₄ Alone: To 1.74 milliliters (3.34 mmoles) of 1.93 molar LiAlH₄ and 18 milliliters of ether was added 5 milliliters (4.46 mmoles, 3 equivalents hydride per mole epoxide) of 0.892 molar ethereal β -diisobutylene oxide. The reaction was carried out in the usual manner. To one reaction mixture was added by direct weighing, 0.323 grams of n-octanol; to the other was added 0.273 grams. The product ratios were determined chromatographically (entry 2, Table 8).

2) One to Four LiAlH₄ to AlCl₃ Reagent: To 14.76 milliliters (11.68 mmoles) of 0.789 molar aluminum chloride solution was added 4.18 milliliters (2.92 mmoles) of 0.698 molar lithium aluminum hydride solution (produces 11.68 mmoles HAlCl₂). A small amount of white precipitate appeared during the mixing of these solutions, which turned black after about two hours. To the above solution was added 2.95 milliliters (0.500 grams, 3.8 mmoles) of an ether solution

containing 0.1694 grams per milliliter of β -diisobutylene oxide. The reaction and workup were carried out in the usual manner. To the gross product was added 0.462 grams of n-octanol. Only one run was made. The product ratios were then chromatographically determined (entry 4, Table 8).

3) One to Three LiAlH_4 to AlCl_3 Reagent: To 11.07 milliliters (8.76 mmoles) of the aluminum chloride solution used above and 5 milliliters of ether was added 4.18 milliliters (2.92 mmoles) of the lithium aluminum hydride solution (produces 11.68 mmoles HAlCl_2). A small amount of white precipitate appeared, which turned black after about two hours. To this solution was added 2.95 milliliters (0.500 grams, 3.8 mmoles) of the above epoxide solution. The reaction and workup were carried out in the usual manner. To the gross product was added 0.462 grams of n-octanol. The product ratios and material balances were then determined (entry 5, Table 8).

4) One to One LiAlH_4 to AlCl_3 Reagent. To 3.69 milliliters (2.92 mmoles) of the above aluminum chloride solution and 15 milliliters of ether was added 4.18 milliliters (2.92 mmoles) of the above lithium aluminum hydride solution (produced 5.84 mmoles H_2AlCl). A small amount of white precipitate appeared, which turned green on standing for two hours. To this solution was added 2.95 milliliters (0.500 grams, 3.8 mmoles) of the above epoxide solution. The reaction and workup were carried out as usual, and 0.462 grams of n-octanol were added. The product ratios were then determined (entry 7, Table 7).

Another set of reductions with this reagent was set up in the following manner: To 5.38 milliliters (3.125 mmoles) of 0.581 molar

aluminum chloride solution and 12 milliliters of distilled ether was added 4.58 milliliters (3.125 mmoles) of 0.683 molar lithium aluminum hydride solution. Two mixed hydride reagents were prepared according to this procedure; one where the solutions were mixed at room temperature (25°C) and the other where the reagent was intermittently cooled in a liquid nitrogen bath during mixing so that the temperature was between -15 degrees and 5 degrees. Infrared spectra of both reagents in diethyl ether solution were obtained and showed the following absorptions:

λ max (microns)	assignment
5.25 (weak)	HAlCl_2
5.40 (strong)	H_2AlCl
5.60 (weak)	AlH_3

The infrared spectra of the mixed hydride prepared at room temperature and the mixed hydride prepared at -15 to five degrees were identical in shape in the 5.0 to 6.0 micron region. To both solutions was added 2.86 milliliters (0.500 grams, 3.8 mmoles) of a β -diisobutylene oxide solution which contained 0.174 grams epoxide per milliliters of solution. The reaction and workup were carried out as usual. To the gross products were added 0.374 grams of n-octanol, and the product ratios were determined (product ratios for the reduction using the mixed hydride reagent generated at low temperature is given in entry 8, Table 7, and those for the reduction using the reagent generated at room temper-

ature is given in entry 9, Table 8).

Another reduction with this reagent was set up in a similar manner. To 16.9 milliliters (5.84 mmoles) of 0.345 molar aluminum chloride solution was added 5.94 milliliters (5.84 mmoles) of 0.983 molar lithium aluminum hydride solution (produces 11.68 mmoles H_2AlCl ; 3 fold molar excess of H_2AlCl over epoxide). To this was added 3.3 milliliters (0.500 grams, 3.8 moles) of a β -diisobutylene oxide solution containing 0.152 grams of epoxide per milliliter of solution. The reaction and workup were carried out in the usual manner. To the gross product was added 0.383 grams of n-octanol, and the product ratios and material balances were determined. Only one run was made (entry 10, Table 7).

5) Three to One LiAlH_4 to AlCl_3 Reagent: To 1.33 milliliters (0.973 mmoles) of 0.79 molar aluminum chloride solution and 15 milliliters of ether was added 4.18 milliliters (2.92 mmoles) of 0.698 molar lithium aluminum hydride (produces 3.8 mmoles AlH_3). Copious amounts of a white precipitate appeared as the solutions were mixed, which did not change color with the passage of time. To this reagent was added 2.95 milliliters (0.500 grams, 3.8 mmoles) of a β -diisobutylene oxide solution containing 0.169 grams of epoxide per milliliter of solution. The reaction and workup were carried out in the usual manner. To the gross product was added 0.462 grams of n-octanol and the product ratios were determined (entry 12, Table 7).

Another reduction was carried out in a similar manner by adding 8.91 milliliters (8.76 mmoles) of 0.983 molar lithium aluminum hydride solution to 8.46 milliliters (2.92 mmoles) of 0.345 molar aluminum

chloride solution and five milliliters of ether (produces 11.68 mmoles AlH_3 , a three-fold molar excess of AlH_3 over epoxide). To this reagent was added 3.3 milliliters (0.500 grams, 3.8 mmoles) of a β -diisobutylene oxide solution containing 0.151 grams of epoxide per milliliter of solution. The reaction and workup were carried out in the usual manner. To the gross product was added 0.383 grams of n-octanol and the product ratios were determined. Only one run was made (entry 13, Table 7).

6) Three to One LiAlH_4 to AlCl_3 Reagent with Excess LiAlH_4 :

To 1.68 milliliters (0.975 mmoles) of 0.581 molar aluminum chloride and 17 milliliters of ether was added 4.58 milliliters (3.125 millimoles) of 0.683 molar lithium aluminum hydride solution (produces 3.8 mmoles AlH_3 , plus 0.205 millimoles excess lithium aluminum hydride). To this solution was added 2.86 milliliters (0.500 grams, 3.8 mmoles) of a β -diisobutylene oxide solution containing 0.175 grams of epoxide per milliliter of solution. The reaction and workup were carried out in the usual manner. To the gross product was added 0.374 grams of n-octanol. The product ratios and material balance were determined (entry 14, Table 8).

7) Pure HALCl_2 : Pure hydridoaluminum dichloride was prepared according to the method of Ashby and Prather¹⁵. To 50 milliliters (26.5 mmoles) of 0.531 molar aluminum chloride solution was added 13.1 milliliters (8.95 mmoles) of 0.683 molar lithium aluminum hydride solution (produces 35.5 mmoles HALCl_2). The ether was removed in vacuo, and benzene was distilled directly into the flask containing the concentrated hydride. The resulting solution was filtered free of solid material and concentrated to dryness in vacuo. The benzene extraction

was repeated twice more. This resulted in the isolation of 3.047 grams (17.7 mmoles, 50 percent yield) of clear liquid with a small amount of solid material, which was probably a hydrolysis product. The pure HAlCl_2 was transferred to a 50 milliliter volumetric flask. Enough ether was added to bring the solution level to the mark.

To a 20 milliliter (7.08 mmoles) portion and a 30 milliliter (10.6 mmoles) portion of the above hydridoaluminum dichloride solution were added 1.8 milliliter (0.273 grams, 2.07 millimoles) portions of a β -diisobutylene solution containing 0.150 grams of epoxide per milliliter. The reaction and workup were carried out as usual. To the gross product was added 0.101 grams of n-octanol. The product ratios and material balances were determined. The product ratios were found to be identical within an absolute percent, so only the average of the two sets of product ratios will be presented (entry 15, table 8).

8) One to Three LiAlD_4 to AlCl_3 Reagent: To 37.0 milliliters (12.8 mmoles) of 0.345 molar aluminum chloride solution was added a 10 or 12 milliliter ether slurry containing 0.179 grams (4.27 mmoles) of lithium aluminum deuteride. The resulting mixture was stirred for 20 to 30 minutes. A white precipitate appeared, which turned black after two hours. To the resulting reagent was added 6.0 milliliters (0.91 grams, 6.91 mmoles) of a β -diisobutylene oxide solution containing 0.152 grams of epoxide per milliliter. The reaction and workup were carried out in the usual manner. About three quarters of the gross product was lost through spillage. An attempt was made to salvage this lost portion. No n-octanol was added and only product ratios were determined (entry 15, Table 7).

About 10 milligrams of 2,4,4-trimethylpentanol-3 (TMPOH-3) and 300 to 400 milligrams of tetramethylbutanol (TMBOH) were collected from repeated injection of 0.1 to 0.2 milliliter samples of the gross product into a six foot column packed with ten percent carbowax 20M under the same conditions as those used for the product determinations. NMR spectra were taken, and compared with those obtained from a sample of undeuterated alcohol isolated by preparative VPC from the reduction involving the one to one LiAlH_4 to AlBr_3 combination. The results are listed in Table 8.

Tetrahydrofuranates and triethylammonates of the various chloride mixed hydride reagents were prepared by mixing aluminum chloride and lithium aluminum hydride solution according to procedures outlined above, and then adding a measured amount of one of the two solvating species listed above. Epoxide was then added and the reaction and workup procedures listed were followed. The following mixed hydride reagents were reacted with β -diisobutylene oxide under these conditions. Duplicate runs were made, unless otherwise stated.

1) One to Three LiAlH_4 to AlCl_3 Reagent as the Tetrahydrofuranate: To 15.1 milliliters (8.78 mmoles) of 0.581 molar aluminum chloride solution was added 4.40 milliliters (3.0 millimoles) of 0.683 molar lithium aluminum hydride solution and 1.77 grams (24.7 mmoles, about a two-fold excess of THF over HALCl_2) of tetrahydrofuran. To this reagent was added 2.86 milliliters (0.500 grams, 3.8 mmoles) of a β -diisobutylene oxide solution containing 0.175 grams of epoxide per milliliter. The reaction and workup were carried out in the usual manner. To the gross product was added 0.374 grams of n-octanol. The

product ratios and material balances were determined (entry 1, table 9).

2) One to One LiAlH_4 to AlCl_3 Reagent as the Tetrahydrofuranate: To 5.62 milliliters (2.98 mmoles) of 0.53) molar aluminum chloride solution and 10 milliliters of ether was added 4.35 milliliters (2.95 mmoles) of 0.683 molar lithium aluminum hydride solution, and 1.2cc (1.26 grams, about 12 millimoles, two-fold molar excess over H_2AlCl) of tetrahydrofuran. To this reagent was added 2.8 milliliters (0.490 grams, 3.8 mmoles) of a β -diisobutylene oxide solution containing 0.175 grams epoxide per milliliter. The reaction and workup were carried out as usual. To the gross product was added 0.284 grams of n-octanol. The product ratios and material balances were determined (entry 2, Table 9).

3) Three to One LiAlH_4 to AlCl_3 Reagent as the Tetrahydrofuranate: To 1.87 milliliters (0.99 mmoles) of 0.531 molar aluminum chloride solution and 15 milliliters of ether was added 4.35 milliliters (2.94 mmoles) of 0.683 molar lithium aluminum hydride solution and 0.82 milliliters (0.86 grams, 8.2 millimoles, two-fold molar excess over AlH_3) of tetrahydrofuran. To this reagent was added 2.8 milliliters (0.491 grams, 3.8 mmoles) of the β -diisobutylene oxide solution described above. The reaction and workup were carried out as usual. To the gross product was added 0.284 grams of n-octanol. The product ratios and material balances were determined (entry 3, Table 9).

4) One to Three LiAlH_4 to AlCl_3 Reagent as the Triethylamminate: To 15.1 milliliters (8.78 millimoles) of 0.581 molar aluminum chloride solution was added 4.40 milliliters (3.0 mmoles)

of 0.683 molar lithium aluminum hydride solution and 3.5 milliliters (2.52 grams, 25 mmoles; two-fold molar excess over HAlCl_2) of triethylamine. To the resulting reagent was added 2.86 milliliters (0.500 grams, 3.8 mmoles) of a β -diisobutylene oxide solution containing 0.175 grams of epoxide per milliliter of solution. The reaction and workup were carried out in the usual manner. To the gross product was 0.374 grams of n-octanol. The product ratios and material balance were determined. Only one run was made (entry 4, Table 7).

Another mixed hydride reagent of this type was prepared using a different ratio of triethylamine to hydridoaluminum chloride (one to one molar ratio). To 15.8 milliliters (8.42 millimoles) of 0.531 molar aluminum chloride solution was added 4.16 milliliters (2.84 mmoles) of 0.683 molar lithium aluminum hydride solution and 1.64 milliliters (1.18 grams, 11.7 millimoles) of triethylamine. To the resulting solution was added 2.9 milliliters (0.491 grams, 3.7 millimoles) of a β -diisobutylene oxide solution containing 0.175 grams of epoxide per milliliter. The reaction and workup were carried out in the usual manner. To the gross product was added 0.284 grams of n-octanol. The product ratios and material balances were determined. Only one run was made (entry 5, Table 7).

5) One to One LiAlH_4 to AlCl_3 Reagent as the Triethylamminate:
To 5.28 milliliters (2.80 mmoles) of 0.531 molar aluminum chloride solution and 10 milliliters of ether was added 4.16 milliliters (2.84 mmoles) of 0.683 molar lithium aluminum hydride solution and 0.82 milliliters (0.59 grams, 5.8 mmoles; one to one molar ratio triethylamine to H_2AlCl). To this reagent was added 2.90 milliliters (0.491

grams, 3.7 millimoles) of a β -diisobutylene oxide solution containing 0.175 grams of epoxide per milliliter of solution. The reaction and workup were carried out as usual. To the gross product was added 0.284 grams of n-octanol. The product ratios and material balances were determined. Only one run was made (entry 6, Table 9).

6) Three to One LiAlH_4 to AlCl_3 Reagent as the Triethyl-
amminate: To 1.76 milliliters (0.935 mmoles) of 0.531 molar aluminum chloride solution and 15 milliliters of ether was added 4.16 milliliters (2.84 mmoles) of 0.683 molar lithium aluminum hydride solution and 0.54 milliliters (0.39 grams, 3.8 mmoles of triethylamine. To the resulting reagent was added 2.90 milliliters (0.491 grams, 3.8 millimoles) of the β -diisobutylene oxide solution described immediately above. The reaction and workup were carried out in the usual manner. To the gross product was added 0.284 grams of n-octanol. The product ratios and material balance were determined. Only one run was made (entry 7, Table 9).

Mixed hydride reductions of β -diisobutylene oxide involving mixtures of lithium aluminum hydride and aluminum iodide in various molar ratios were carried out by exactly the same types of procedures as used for those using reagents prepared with lithium aluminum hydride and aluminum chloride. The reductions were exothermic. The analytical data for the various solutions used is shown below.

$$[\text{LiAlH}_4] = 0.998\text{M} \quad [\text{AlI}_3] = 0.698\text{M}$$

$$\text{Al:I} = 1:2.90$$

$$[\text{epox.}] = 0.169 \text{ gram/ml.}$$

Reductions using the following reagents were carried out in β -diisobutylene oxide. Duplicate runs were made in both cases.

1) One to Three LiAlH_4 to AlI_3 Reagent: To 15.5 ml (8.76 mmoles) of the above aluminum iodide solution and 5 milliliters of ether was added 2.93 milliliters (2.92 mmoles) of the above lithium aluminum hydride solution (produces 11.68 mmoles HAlI_2). To the resulting reagent was added 2.96 milliliters (0.500 grams, 3.8 mmoles) of the β -diisobutylene oxide solution. The reaction and workup were carried out as usual. The crude product was brown, presumably from the presence of free iodine. To the gross product was added 0.212 grams of n-octanol. The product ratios and material balances were determined (entry 3, table 10).

2) One to One LiAlH_4 to AlI_3 Reagent: To 4.18 milliliters (2.92 mmoles) of the aluminum iodide solution and 15 milliliters of ether was added 2.93 milliliters (2.92 mmoles) of the lithium aluminum hydride solution (produces 5.84 mmoles H_2AlI). To the resulting reagent was added 2.96 milliliters (0.500 grams, 3.8 mmoles) of the β -diisobutylene oxide solution. The reaction and workup were carried out in the usual manner. The gross product was brown, presumably from the presence of free iodine. To the gross product was added 0.212 grams of n-octanol. The product ratios, and material balances were determined (entry 4, Table 10).

The mixed hydride reductions of β -diisobutylene oxide involving mixtures of lithium aluminum hydride and aluminum bromide in various molar ratios were carried out by using a slightly different procedure. The solutions were introduced into a flame-dried flask under a dry

nitrogen atmosphere through a rubber serum cap by means of an appropriately sized flame-dried and nitrogen purged hypodermic syringe. The reductions were exothermic. The analytical data for the various solutions is presented below.

$$\begin{array}{ll} [\text{LiAlH}_4] = 0.866\text{M} & [\text{AlBr}_3]_{-10^\circ\text{C}} = 0.633\text{M} \\ [\text{epox}] = 0.152 \text{ grams/ml} & \text{Al:Br} = 1:3.03 \end{array}$$

The aluminum bromide solution was red, presumably because a trace amount of free bromide was present. The reaction conditions and work-up procedures are the same as those used for the other reductions performed on this epoxide. Reductions using the following reagents were carried out on β diisobutylene oxide:

1) One to Three LiAlH_4 to AlBr_3 Reagent: To 13.9 milliliters (8.79 mmoles) of the aluminum bromide solution, and 5.0 milliliters of ether was added 3.4 milliliters (2.93 millimoles) of the lithium aluminum hydride solution (produces 11.72 mmoles HALBr_2). The red color due to the free bromine in the aluminum bromide solution disappeared after the addition of the first two or three drops of hydride solution. To the clear reagent was added 3.3 milliliters (0.500 grams, 3.8 mmoles) of the β -diisobutylene oxide solution. The reaction and workup were carried out in the usual manner. To the gross product was added 0.383 grams of n-octanol. The product ratios and material balances were determined. Only one run was made (entry 1, Table 10).

2) One to One LiAlH_4 to AlBr_3 Reagent: To 4.6 milliliters (2.93 mmoles) of the aluminum bromide solution and 13 milliliters of ether was added 3.4 milliliters (2.93 millimoles) of the lithium

aluminum hydride solution. To the resulting clear reagent was added 3.3 milliliters (0.500 grams, 3.8 mmoles) of the epoxide solution. The reaction and workup were carried out in the usual manner. To the gross product was added 0.383 grams of n-octanol. The product ratios and material balances were determined. Two runs were made (entry 2, Table 10).

Reductions of β -diisobutylene oxide with the alkoxyaluminum hydrides were carried out in the following manner. First an aluminum hydride in tetrahydrofuran solution was prepared from 100 percent sulfuric acid and lithium aluminum hydride in tetrahydrofuran by Mr. John Lott according to the method of Brown and Yoon¹⁹ (equation 22, page 9). The 100 percent sulfuric acid was prepared by mixing fuming sulfuric acid and concentrated sulfuric acid until the freezing point of the solution reached a certain specific value. Then a measured amount of the 100 percent sulfuric acid was slowly added to the lithium aluminum hydride solution under nitrogen. The resulting aluminum hydride solution was stored in the refrigerator, and standardized at 0 degrees centigrade. An aluminum analysis yielded the following data:

$$[\text{Al}]_{\text{tot}} = [\text{AlH}_3] = 0.599\text{M}$$

Alkoxyaluminum hydrides were prepared by Mr. John Lott according to the method of Suchi²⁰. A measured amount of aluminum hydride solution was withdrawn with a flame-dried hypodermic syringe and introduced through a serum cap into a flame-dried flask ice-cooled under a dry

nitrogen atmosphere. An equimolar amount or two-fold molar excess of the appropriate alcohol was introduced in the same manner, followed by an amount of tetrahydrofuran sufficient to bring the reaction mixture up to a certain standard volume. A measured amount of β -diisobutylene oxide in tetrahydrofuran was then added. Then the reaction mixture was either allowed to stand for two hours (normal conditions) or refluxed for six hours (forcing conditions). After the appropriate time elapsed, 10.0 milliliters of water, and an amount of dilute mineral acid sufficient to dissolve most of the basic aluminum salts was carefully added to the reaction mixtures. The hydrolyzed reaction mixture was then extracted with two approximately ten milliliter portions of petroleum ether and one ten milliliter portion of diethyl ether. The organic layers were combined and dried over anhydrous potassium carbonate. A measured amount of n-octanol in ether was added, and the gross product solution was concentrated in vacuo to about one tenth of its original volume. The product ratios and material balances were then determined chromatographically. This procedure was used for the reduction of β -diisobutylene oxide with the following reagents:

1) AlH_3 in THF: To 6.52 milliliters (3.9 millimoles) of 0.599 molar aluminum hydride in tetrahydrofuran and 14 milliliters of tetrahydrofuran was added 3.0 milliliters (0.500 grams, 3.8 mmoles) of β -diisobutylene oxide in tetrahydrofuran which contained 0.167 grams of epoxide per milliliter of solution. The reaction was carried out only under normal conditions. To the crude product was added 0.157 grams of n-octanol and the product ratios and material balances were determined. Duplicate runs were made (entry 1, Table 11).

2) $\text{AlH}_2(\text{O-t-Bu})$ in THF: To 9.8 milliliters (5.83 mmoles) of the above aluminum hydride solution was added 0.55 milliliters (5.85 mmoles^{*}) of t-butanol and 13 milliliters of tetrahydrofuran (produces 5.85 mmoles $\text{H}_2\text{AlO-t-Bu}$). To this solution was added 3.0 milliliters (0.500 grams, 3.8 mmoles) of the above epoxide solution. The reaction was carried out under both normal and forcing conditions. The reaction mixtures were worked up in the usual manner. To the gross product of the reaction run under normal conditions was added 0.157 grams of n-octanol and to the one run under forcing conditions was added 0.383 grams of n-octanol. The product ratios and material balances were determined (normal conditions, entry 2, Table 11; forcing conditions, entry 3, Table 11).

3) $\text{AlH}(\text{O-t-Bu})_2$ in THF: To 19.6 milliliters (11.70 mmoles) of the above aluminum hydride solution was added 2.2 milliliters of t-butanol (23.4 mmoles) and 5.0 milliliters of tetrahydrofuran (produces 11.70 mmoles $\text{HAl}(\text{O-t-Bu})_2$). To the resulting reagents was added 3.0 milliliters (0.500 grams, 3.8 mmoles) of the β -diisobutylene oxide solution listed above. The reaction mixtures were worked up in the usual manner. To the gross product of the reaction run under normal conditions was added 0.157 grams of n-octanol. To the one run under forcing conditions was added 0.383 grams of n-octanol. The product ratios and material balances were determined (normal conditions, entry

* Volumes required to make up a certain molar quantity of the alcohols used were calculated from density values given in Handbook of Chemistry and Physics, Charles D. Hadgman, ed. 39th Edition, 1957-58, Chemical Rubber Publishing Co., Cleveland Ohio, 1958.

4, Table 11; forcing conditions, entry 5, Table 11).

4) $\text{AlH}_2(\text{O-i-Pr})$ in THF: This reaction mixture was prepared from the same volumes of the hydride and epoxide solutions as were used for the reductions involving t-butoxyaluminum hydride. To the aluminum hydride solution was added 0.45 milliliters (5.85 mmoles) of isopropanol (produces 5.85 mmoles $\text{AlH}_2(\text{O-i-Pr})$). The reaction was run under both normal and forcing conditions, and the workups were carried out in the usual manner. To both gross products were added 0.383 grams of n-octanol (normal conditions, entry 6, Table 11, forcing conditions, entry 7, Table 11).

5) $\text{AlH}(\text{O-i-Pr})_2$ in THF: This reaction mixture was prepared from the same amounts of the hydride and epoxide solutions as were used for the reduction involving di-t-butoxyaluminum hydride. To the aluminum hydride solution was added 1.79 milliliters (23.4 mmoles) of isopropanol (produces 11.7 mmoles $\text{AlH}(\text{O-i-Pr})_2$). The reaction was run under both normal and forcing conditions, and the workups were carried out in the usual manner. To both reactions mixtures were added 0.383 grams of n-octanol (normal conditions, entry 7, Table 11; forcing conditions, entry 8, Table 11).

6) AlH_2OMe in THF: This reduction mixture was prepared from the same amounts of hydride and epoxide solutions as were used for the reductions involving t-butoxyaluminum and isopropoxyaluminum hydrides. To the aluminum hydride solution was added 0.24 milliliters (5.85 mmoles) of methanol. Copious amounts of a white solid appeared as the alcohol was added. The reaction was run only under normal conditions. To the gross product was added 0.383 grams of n-octanol.

The product ratios and material balance were determined (entry 9, Table 11).

7) AlH(OMe)_2 in THF: This reduction mixture was prepared from the same amounts of hydride and epoxide solutions as were used for the reductions involving di-t-butoxy- and diisopropoxyaluminum hydride. To the aluminum hydride solution was added 0.96 milliliters (23.4 mmoles) of methanol (produces 11.7 mmoles AlH(OMe)_2). Copious amounts of a white solid appeared as the alcohol was added. The reduction was run under both normal and forcing conditions. To both gross products were added 0.383 grams of n-octanol. The product ratios and material balances were determined (normal conditions, entry 10, Table 11; forcing conditions, entry 11, Table 11).

The product ratios and material balances from the above reductions will be presented in tabular form in the next chapter. Conclusions will be drawn concerning the steric and electronic effects on the course these reactions take and on the nature of and role played by the various reactive species in the mechanisms by which these mixed hydride reagents react with organic functional groups.

CHAPTER VI

RESULTS AND DISCUSSION

The data obtained from the study of the products and product ratios from the mixed hydride reductions of styrene oxide, triphenylethylene oxide, exo-norbornene oxide and β -diisobutylene oxide will now be presented and discussed.

The product ratios from the mixed hydride reductions of styrene oxide are in good agreement, with earlier work¹¹, as can be seen by inspection of the data in Table 7. There is no significant difference in the product ratios between those arising from the one to three or one to four lithium aluminum hydride to aluminum chloride reagents. It appears, therefore that the excess aluminum chloride in the one to four reagent does not play a significant role in the mechanism by which this reagent reacts with styrene oxide. (Data to be presented later shows that this is the case also for reductions of β -diisobutylene oxide involving the one to four reagent.) However it was decided during the course of this work that styrene oxide does not adequately meet the requirements outlined in chapter I. Of the two products which arise from reductions of styrene oxide, one, 2-phenylethanol, can arise by two distinctly different pathways:

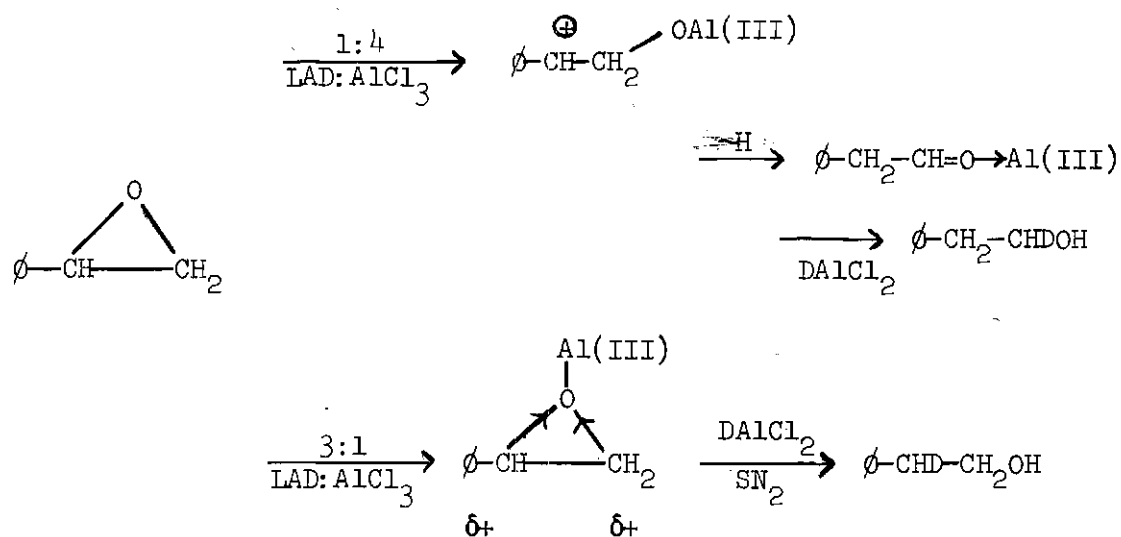


Table 7. Product Ratios from Reductions of Styrene Oxide by Various Lithium Aluminum Hydride-Aluminum Chloride Combinations.^a

Entry No.	Ratio of LAH:AlCl ₃	Styr. Ox. (% Yield)	φCHOHCH ₃	φCH ₂ CH ₂ OH	Gross Prod. Yield (%)	Ref.
1	LAH alone	-	90-95	5-10	82	12
2	LAH alone	-	91	9	91	b
3	1:4	-	2-5	95-98	71	12
4	1:4	13	2	98	64	b
5	1:3	10	1	99	69	b

a) One equivalent hydride per mole epoxide

b) This work.

The fraction of this product arising from each of these pathways could most easily be determined by using lithium aluminum deuteride to prepare the mixed hydrides, isolating the 2-phenylethanol formed, and determining the extent of deuteration at each of the reaction sites by NMR measurements. For a study of the scope outlined in chapter I, use of lithium aluminum deuteride would be economically unfeasible.

Data from earlier work already cited²² indicates that mixed hydride reductions of triphenylethylene oxide might yield more meaningful data. There are more products formed, and the product ratios seem to be fairly sensitive to the properties of the mixed hydride used. Also, the mode of formation of most of the products can be unambiguously assigned. The early workers obtained their product ratios by separating and isolating the products by column chromatography. Vapor-phase chromatography data would be expected to yield more precise data, so an attempt was made to find conditions by which gross products from mixed hydride reductions performed on this epoxide could be analyzed by this method. However, triphenylethylene oxide and its three alcoholic reduction would not pass through columns packed with any of the substrates at hand except under the rather drastic conditions listed in Table five. At these high temperatures and unusually high helium flow rates, separation of the alcoholic reduction products sufficient for product identification and analysis was not obtained with any of the columns tried. All plans for studying this system were abandoned.

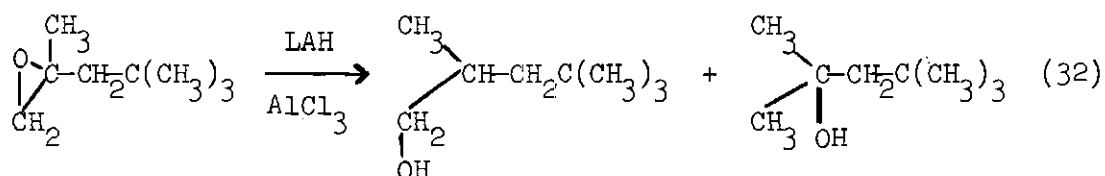
The work on the mixed hydride reductions of exo-norbornene oxide is still incomplete. The major product arising from all of the mixed hydride reductions is the component listed as (d) in Table four

above. It, as well as some of the minor components, has not been identified. It is not one of the three possible norbornyl alcohols, which were the only products initially expected. It is evidently the result of some gross rearrangement of the norbornane skeleton. The work done on this system should be completed. Also, a product study on the rearrangement of exo-norbornene oxide catalyzed by Lewis acids of varying strength, such as magnesium bromide, the aluminum halides, and boron trifluoride diethyletherate, might yield interesting results. Early work previously cited showed that magnesium bromide-catalyzed isomerizations of epoxides involve a cyclic magnesium bromide-epoxide complex²³ as shown in Figure 1, while boron trifluoride catalyzed isomerization of epoxides involves free carbonium ions. The results of the study of mixed hydride reductions of exo-norbornene oxide coupled with a study of the products resulting from an isomerization of this epoxide catalyzed by the Lewis acids mentioned above might furnish new information on the much studied carbonium ion chemistry of the norbornyl system.

By far the greatest amount of meaningful data on the mechanism of mixed hydride reductions was furnished by the study of the reductions of β -diisobutylene oxide. A few preliminary remarks concerning this phase of the study will now be presented.

First of all, it should be remembered that this epoxide as used for these reductions was only 97 percent pure, even after two careful distillations using a spinning band column. The three percent impurity is probably the oxide of the terminal olefin, α -diisobutylene.

When this epoxide is treated with a mixed hydride, two products can be obtained. These are 2,4,4-trimethylpentanols-1 and -2¹¹. In the reductions of β -diisobutylene oxide involving the more strongly acidic mixed hydride reagents, another component, besides the four mentioned on page 13, is formed in about a two to three percent yield. It was not identified, but probably arises from the α -diisobutylene oxide, and probably is 2,4,4-trimethylpentanol-1. Since 2,4,4-trimethylpentanol-2 can arise from both α - and β -diisobutylene oxide, its detection in yields of less than three percent can not be unambiguously interpreted. For this reason, the ratios of yields of trimethylpentanol-2 to trimethylpentanol-3 arising from the reduction of β -diisobutylene oxide,



which will be presented in tabular form below should be considered as an upper limit.

The second fact that should be noted is that the reactions of mixed hydride reagents with this epoxide are all exothermic. In the case of all hydridoaluminum halides, the solvent refluxed vigorously as epoxide solution was added to the mixed hydride solution. In the case of aluminum hydride, the solvent began to reflux a few seconds after the addition of epoxide was complete. In all cases, refluxing of the solvent subsided after a very few minutes. The process of going from a strained, cyclic starting material to

acyclic products could account for most of the released energy. However, an acid-base complexation reaction between the acidic aluminum species and the oxygen of the oxirane ring could also explain this phenomena. In any case, solvent reflux can be considered as an indication that some fairly rapid reaction is occurring.

The data from the mixed hydride reductions of β -diisobutylene oxide will now be presented. Duplicate runs were set up in most cases, except as noted in the tables. The product ratios presented are the average from two runs. In all cases except those specifically noted, the average deviation in these ratios was at most one or two absolute percent. The data shows that the following pathways are probably operative:

Table 8. Product Ratios From the Reduction of β -diisobutylene Oxide With Various Lithium Aluminum Hydride-Aluminum Chloride Combinations^a in Diethyl Ether

entry no.	ratio of LAH:AlCl ₃	TMPOH-2	TMPOH-3	Δ -1-TMPOH-3	TMBOH	gross product yield	ref.
1	LAH alone	100	-	-	-	21%	11
2	LAH alone ^c	-	-	-	-	-	b
3	1:4	-	15	8	77	83%	22
4	1:4 ^e	< 1	16	9	74	84%	b
5	1:3	< 1	16	9	74	85%	b
6	1:1	14	32	9	45	95%	24
7	1:1	2	24	8	65	91-93%	b
8	1:1, L.T. ^e	2	26	10	62	93%	b
9	1:1, R.T. ^e	2	24	10	64	85%	b
10	1:1 ^{d,e}	3	31	6	60	92%	b
11	3:1	36	50	10	4	96%	24
12	3:1	12	34	45	9	95-98%	b
13	3:1 ^{e,f}	19	55	21	5	84%	b
14	3.2:1 ^e	28	59	10	3	85%	b
15	HA1Cl ₂	< 1	11	8	80	80-89%	b
16	1:3 LAD: AlCl ₃	< 1	11	8	80	-	b

- a) three equivalents hydride per mole epoxide, unless otherwise stated; the product ratios are the average of two determinations unless otherwise stated.
- b) this work.
- c) Only starting material was detected. The amount present was not determined.
- d) three moles of H₂AlCl per mole of epoxide.
- e) Only one run was made.
- f) three moles of AlH₃ per mole of epoxide.

Table 9. Product Ratios^a from the Reduction of β -diisobutylene Oxide With Various Lithium Aluminum Hydride-Aluminum Chloride Combinations^b as Tetrahydrofuranates^c and Triethylamminates^a.

entry no.	ratio of LAH:AlCl ₃	TMPOH-2	TMPOH-3	Δ -1-TMPOH-3	TMBOH	gross product yield
1	1:3, THF	2	27	9	61	75-78%
2	1:1, THF	11	50	7	31	97-100%
3	3:1, THF	30	58	11	1	105-106%
4	1:3, NET ₃ ^d	-	12	17	71	100%
5	1:3, NET ₃ ^{e, f}	-	8	40	52	56%
6	1:1, NET ₃ ^e	1	20	17	65	101%
7	3:1, NET ₃ ^e	21	44	32	3	70%

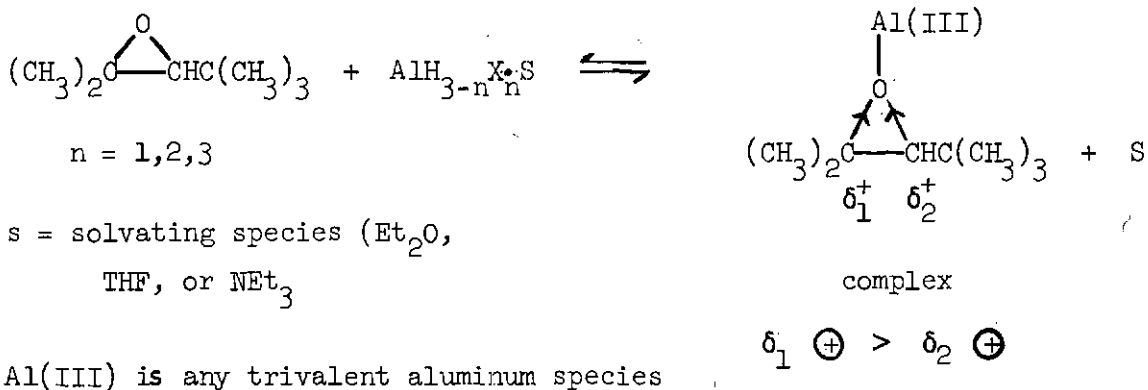
- a) The product ratios are an average from two runs, unless otherwise stated.
- b) three equivalents of hydride per mole of epoxide
- c) two moles of tetrahydrofuran per mole of aluminum species.
- d) one mole of triethylamine per mole of aluminum species, unless otherwise stated.
- e) Only one run was made.
- f) two moles of triethylamine per mole of epoxide.
- g) 30 percent yield of starting material was also detected.

Table 10. Product Ratios From the Reduction of β -diisobutylene Oxide With Various Lithium Aluminum Hydride-Aluminum Bromide or Iodide Combinations^a.

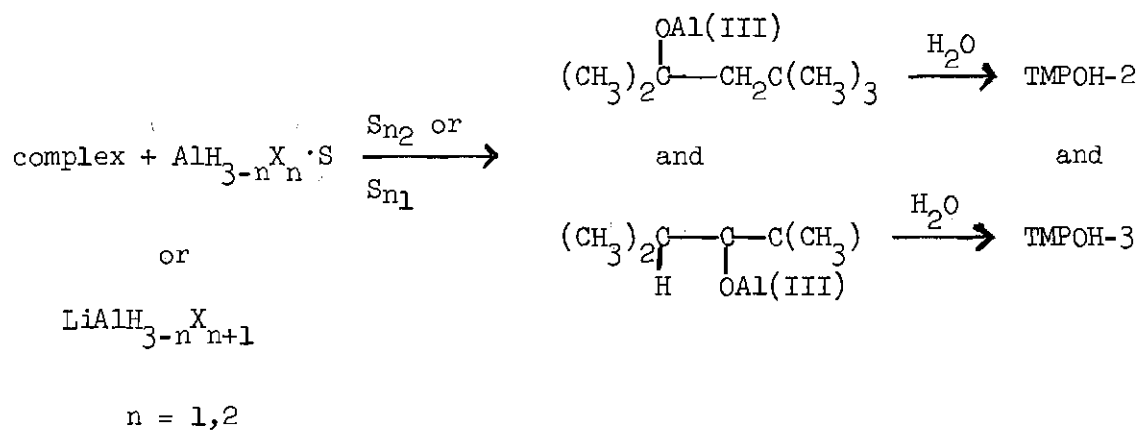
entry no.	ratio of LAH:AlCl ₃	TMPOH-2	TMPOH-3	Δ -1-TMPOH-3	TMBOH	gross product yield
1	1:3, Br	1	19	15	65	83-86%
2 ^b	1:1, Br	5	44	7	44	89%
3	1:3, I	3	23	20	54	73-89%
4	1:1, I ^e	-	33	32	35	88-90%

- a) three equivalents hydride per mole epoxides; The product ratios are average values from two determinations, unless otherwise stated.
- b) Only one run was made.
- c) Average deviation of plus or minus three absolute percent in the product ratios of TMPOH-3 and TMBOH.

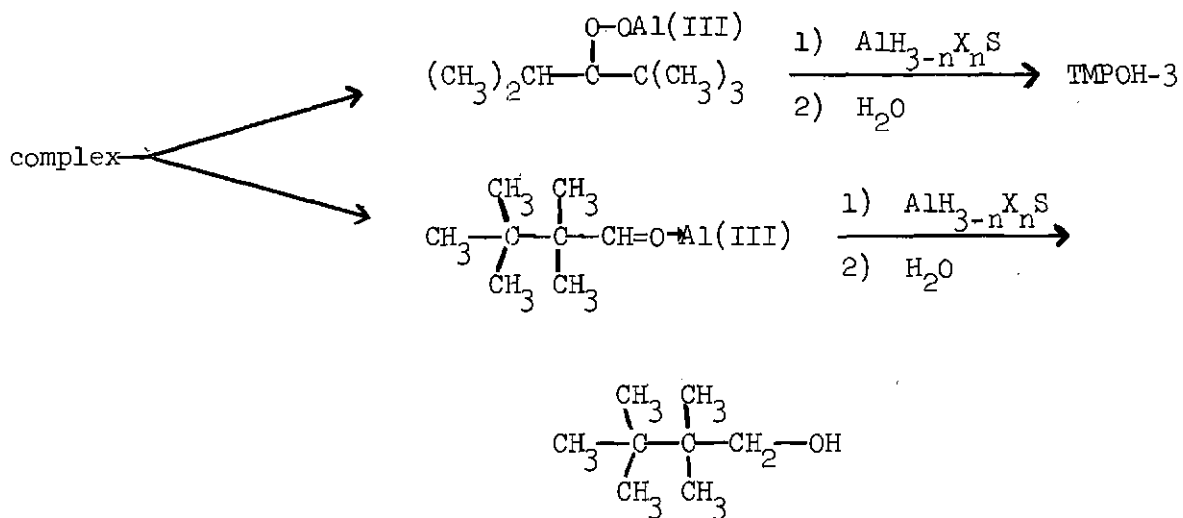
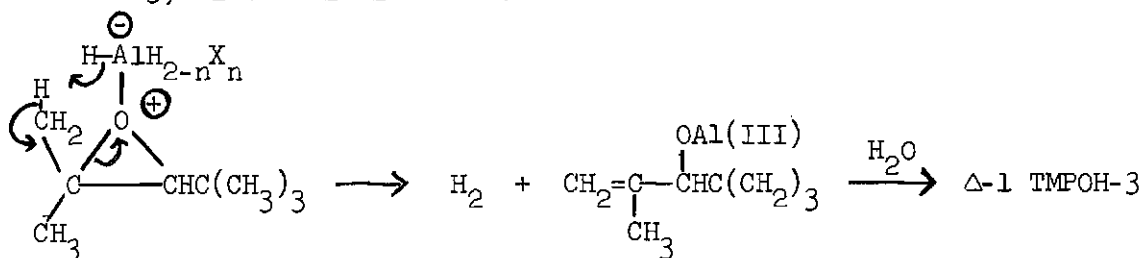
1) complexation



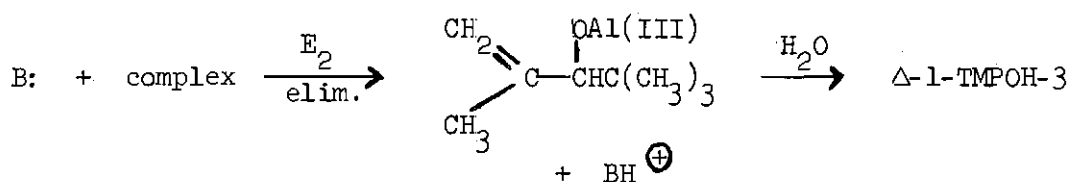
2a) Direct reduction



2b) Migration and Subsequent Reduction

3) Internal Elimination²⁴

4) Base-catalyzed Elimination



That prior complexation is necessary to activate this rather sterically hindered epoxide sufficiently so that reduction can take place is shown by the following facts: The reaction of β -diisobutylene oxide with any mixed hydride is complete within a few minutes. The epoxide is inert to lithium aluminum hydride, however, at least under the conditions used in this work (entry 2, Table 8). It would be expected that lithium aluminum hydride should be a better hydride donor than any of the acidic (and electron deficient) hydridoaluminum halides, so the reducing power of the hydride involved cannot be the only important factor in these reactions. The role of the Lewis acid in step one is to complex with the oxirane oxygen and at least partially polarize the carbon-oxygen bonds in the oxirane ring. This, of course leaves the carbons somewhat electron deficient, and therefore much more labile to attack by a hydride donor.

The strength of the mixed hydride as a Lewis acid determines the degree of polarization of the carbon-oxygen bonds, and therefore the type of mechanism operative in the direct reduction pathway. In the case of weak Lewis acids, such as the three to one lithium aluminum hydride to aluminum chloride, reagent (AlH_3), direct reduction occurs by an acid-assisted $\text{S}_{\text{N}}2$ pathway (where bond breaking has occurred

to a greater extent than bond formation in the transition state³²). In the case of mixed hydride of stronger Lewis acidity such as the one to three (entry 5, Table 8) or one to four (entry 4, Table 8) lithium aluminum hydride to aluminum chloride reagent, direct reduction probably occurs by an Sn_1 pathway involving a transition state in which the oxirane ring is essentially fully cleaved and there is a virtually full positive charge at the reaction site (bond formation has occurred only negligibly in the transition state). On this basis, the ratio of trimethylpentanol-2, the product favored by steric control, to trimethylpentanol-3, the product favored by carbonium ion stability, would be expected to decrease as the Lewis acidity of the mixed hydrides increases. This trend is indeed observed as the data in Table 11 indicates. This ratio is also a function of the reducing power of the mixed hydride species when bond formation has occurred to a significant extent in the transition state. It would be expected that this ratio would increase as the reducing power of the mixed hydride increases. Comparison of the data from the reductions involving a mixed hydride as the diethyl etherate with the data from the reductions involving the same mixed hydride as a tetrahydrofuranate or triethylamminate shows that this trend is indeed observable (compare entries 1, 11 and 14, Table 12, and entries 5 and 11, Table 11).

If the mixed hydride is a strong enough Lewis acid to completely open the oxirane ring, leaving a full positive charge on one of

32. J. Hine, Physical Organic Chemistry, 2nd Ed., McGraw-Hill Publishing Co., New York, N. Y., 1962, pp. 157-185.

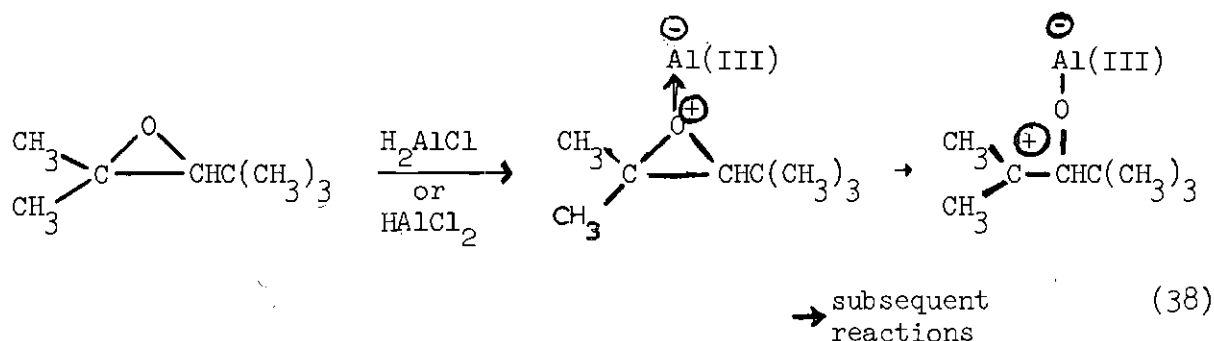
Table 11. Ratio of TMPOH-2 to TMPOH-3^a Arising from Mixed Hydride Reductions of β -diisobutylene Oxide.

Entry No.	Previous Table	Entry No. from Prev. Table	Reducing Agent	TMPOH-2/TMPOH-3
1	8	1	LAH alone ^b	very large
2	8	13	3:1 LAH:AlCl ₃	0.35
3	8	12	3:1 LAH:AlCl ₃	0.35
4	10	2	1:1 LAH:AlBr ₃	0.11
5	8	7	1:1 LAH:AlCl ₃	0.083
6	8	10	1:1 LAH:AlCl ₃	0.097
7	10	3	1:3 LAH:AlI ₃	0.13
8	10	1	1:3 LAH:AlBr ₃	0.05
9	8	5	1:3 LAH:AlCl ₃	< 0.06
10	9	3	3:1 LAH:AlCl ₃ , THF	0.52
11	9	2	1:1 LAH:AlCl ₃ , THF	0.22
12	9	1	1:3 LAH:AlCl ₃ , THF	0.07
13	9	7	3:1 LAH:AlCl ₃ , NEt ₃	0.48
14	9	6	1:1 LAH:AlCl ₃ , NEt ₃	~ 0.05

^aThe value of this ratio was not corrected for the amount of TMPOH-3 arising from a hydride shift (see subsequent discussion).

^bref. 24

the carbons, then another reaction pathway can begin to become prevalent. This pathway is the migration and subsequent reduction shown in step 2b) above. It would be expected that, as the Lewis acidity of the mixed hydride increases (and the reducing power decreases), the yield of tetramethylbutanol (TMBOH), the product of a t-butyl shift and subsequent reduction of the resulting aldehydic intermediate would increase at the expense of the yield of products arising from direct reduction. Inspection of tables eight through eleven shows that this is indeed the case. Inspection of the data in Table 11 shows that virtually all mixed hydride reductions involving a hydrido-aluminum halide result in small values for the ratio of the yield of trimethylpentanol-2 to the yield of trimethylpentanol-3. This indicates that a species of intermediate acidity, such as the one to one lithium aluminum hydride to aluminum chloride reagent (H_2AlCl with some LiCl) is a strong enough Lewis acid to essentially cleave the oxirane ring. The complex in this case (and of course in cases involving more strongly acidic mixed hydride) has considerable carbonium ion character as shown below^{22,24}:



Reactions involving these mixed hydrides can be thought of as involving a trapping of the carbonium ion by hydride donors concurrently with the rearrangements which can occur. The ratio of direct reduction product yields to migration product yield should be related to the reducing power of the mixed hydride reagent. If the mixed hydride reagent is an efficient hydride donor, it should be able to trap the carbonium ion before it can rearrange. A fairly good measure of this reducing power should be the ratio of yields of trimethylpentanol-3 to tetramethylbutanol produced from the various mixed hydride reductions. These ratios will be presented in Table 12.

These results cannot be unambiguously determined, however, because, as shown in equation (33), trimethylpentanol-3 can arise by both the direct reduction and migration pathways. Some reliable experiment needs to be done to determine the amounts of trimethylpentanol-3 arising from each pathway. In other words, the relative migratory aptitudes of the t-butyl group and hydrogen must be determined. Data presented earlier²² (eq. 28, page 11) shows that the product ratios from aluminum chloride and aluminum bromide catalyzed rearrangements of triphenylethylene oxide are identical. It is therefore probable that the ratio of the amount of trimethylpentanol-3 arising from a hydride shift and subsequent reduction to the amount of tetramethylbutanol, which arises by a t-butyl shift and subsequent reduction should be constant, i.e., the relative migratory aptitudes of hydrogen and t-butyl should be constant in all reductions involving the acidic hydridoaluminum halides. There are at least two methods by which this ratio should be determined. Previous workers²² reacted β -diisobutylene oxide with

Table 12. Ratio of TMPOH-3 to TMBOH Arising from Mixed Hydride Reductions of β -diisobutylent Oxide.

Entry No.	Previous Table	Entry No. from Prev. Table	Reducing Agent	TMPOH-3/TMBOH
1	8	12	3:1 LAH:AlCl ₃	3.8
2	10	4	1:1 LAH:AlI ₃	0.94
3	10	2	1:1 LAH:AlBr ₃	1.0
4	8	7	1:1 LAH:AlCl ₃	0.37
5	10	3	1:3 LAH:AlI ₃	0.43
6	10	1	1:3 LAH:AlBr ₃	0.29
7	8	5	1:3 LAH:AlCl ₃	0.22
8	8	4	1:4 LAH:AlCl ₃	0.22
9	8	15	pure HAlCl ₂	0.22
10	8	16	1:3 LAD:AlCl ₃	0.14
11	9	3	3:1 LAH:AlCl ₃ , THF	58.0
12	9	2	1:1 LAH:AlCl ₃ , THF	1.6
13	9	1	1:3 LAH:AlCl ₃ , THF	0.44
14	9	7	3:1 LAH:AlCl ₃ , NEt ₃	14.7
15	9	6	1:1 LAH:AlCl ₃ , NEt ₃	0.31
16	9	5	1:3 LAH:AlCl ₃ , NEt ₃	0.15

aluminum chloride and reported the isolation of crude 2,2,3,3-tetramethylbutyraldehyde in 100 percent yield. However, the way that the experiment was carried out does not rule out the formation of a small amount of 2,4,4-trimethylpentanone-3, which could have escaped detection. A check on this experiment using a more accurate method of product analysis such as vapor phase chromatography should yield a reasonably accurate ratio for the migratory aptitude of hydrogen to that of t-butyl. Another method would be to perform a reduction on β -diisobutylene oxide using a one to three lithium aluminum deuteride to aluminum chloride mixture, analyze the mixture in the usual manner to determine the product ratios, isolate the trimethylpentanol-3 by preparative vapor phase chromatography and run an NMR spectrum to determine the extent of deuteration at each of the two possible reduction sites. This would furnish all of the data necessary to calculate the amount of trimethylpentanol-3 arising from each pathway for the reductions involving all of the hydridoaluminum halides. The latter experiment was chosen as the method by which the relative migratory aptitudes of hydrogen aptitudes of hydrogen and t-butyl would be determined. The experiment outlined above was carried out. The NMR spectra of the deuterated trimethylpentanol-3 was compared with that of the non-deuterated alcohol. The results of this experiment are presented in Table 13, as is the calculated value for the ratio of the migratory aptitude of hydrogen to that of t-butyl. The percentages of trimethylpentanol-3 arising from direct reduction of β -diisobutylene oxide by all of the mixed hydrides were calculated from the product ratios presented earlier and the above ratio. These results are

Table 13. NMR Data On TMPOH-3 Isolated from the Reductions of B-Diisobutylene Oxide with the 1:3 $\text{LiAlD}_4\text{:AlCl}_3$ and $\text{LiAlH}_4\text{:AlCl}_3$ Reagents.

Compound	Absorption (τ)	Multiplicity	No. of Protons	Assignment
TMPOH-3 ^{a,b} (non deuterated)	9.15 ppm	Doublet and Singlet	~ 15	$\text{CH}_3\text{—O—}$
	8.1 ppm	Complex Multiplet	1	CH—
	6.8 ppm	Doublet	1	CH—O—
TMPOH-3 ^c deuterated	9.15 ppm	Doublet and Triplet	~ 15	$\text{CH}_3\text{—C—}$
	-	Complex Multiplet	-	CH—
$\frac{\text{TMPOH-3 mig}^d}{\text{TMBOH}} =$				
0.076 \pm 0.007	6.8 ppm	Broad Singlet	~ 0.05- 0.06	CH—O—
	8.5 ppm (dilute solution)	Broad Singlet	1	O—H

^aThe spectra was taken after addition of $\text{CF}_3\text{CO}_2\text{H}$ in order that no hydroxyl proton resonance is observed.

^bThe solvent is CDCl_3 .

^cThe solvent is CCl_4 .

^dCalculated from percent of deuteration at the carbinol carbon and the product ratios given in entry 16, Table 8.

presented in Table 14, along with the calculated ratios of the amounts of trimethylpentanol-3 arising from direct reduction to the amounts of migration products. The NMR spectra of the deuterated alcohol were not very well defined, however. This was presumably due to the fact that a very small amount of the desired alcohol was isolated. The results presented in Tables 13 and 14 are therefore very much open to question, and this phase of the work should be repeated. The data from Table 12 is reliable, however, and shows the same trends. These results will now be interpreted.

From inspection of the data from reductions involving the dihydridoaluminum halides and hydridoaluminum dihalides, one notes that varying the halide from chloride to bromide to iodide increases the ratio of yields of direct reduction products to migration products, which indicates an increase in the reducing power as the stated variations are made. This is to be expected from the relative electronegativities of the halides. That this variation is somewhat small can be explained by considering the increase in bulk of the mixed hydride attendant with varying the substituent from chloride to bromide to iodide. On steric grounds, one would expect the reactivity as a reducing agent to decrease as this variation of substituents from small to large is made. Evidently electronic effects outweigh effects in these cases.

One of the stated goals of this work was to determine the role played in the reduction of epoxides by each of the species present in the one to four lithium aluminum hydride to aluminum chloride com-

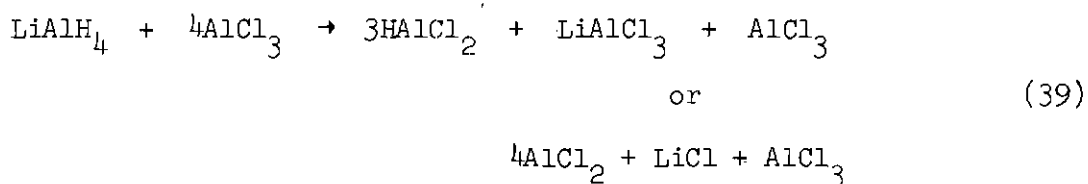
Table 14. Calculated Results of TMPOH 3 dir. red./TMPOH-3 tot., and the Ratios of TMPOH-3 dir. red Migr. Products^a from Various Mixed Hydride Reductions

Entry No.	Old Entry No.	Mixed Hydride	TMPOH-3 dir. red/ TMPOH-3 tot X 100 (%)	TMPOH-3 dir. red, Migration Prods.
1	12, table 8	3:1 LAH:AlCl ₃	> 99	b
2	4, table 10	1:1 LAH:AlI ₃	92	0.80
3	2, table 10	1:1 LAH:AlBr ₃	93	0.86
4	7, table 8	1:1 LAH:AlCl ₃	80	0.27
5	3, table 10	1:3 LAH:AlI ₃	82	0.32
6	1, table 10	1:3 LAH:AlBr ₃	74	0.20
7	5, table 8	1:3 LAH:AlCl ₃	65	0.13
8	4, table 8	1:4 LAH:AlCl ₃	65	0.13
9	15, table 8	pure HAlCl ₂	45	0.06
10	16, table 8	1:3 LAD:AlCl ₃	45	0.06
11	3, table 9	3:1 LAH:AlCl ₃ , THF	> 99	b
12	2, table 9	1:1 LAH:AlCl ₃ , THF	95	1.4
13	1, table 9	1:3 LAH:AlCl ₃ , THF	83	0.34
14	7, table 9	3:1 LAH:AlCl ₃ , NEt ₃	> 99	b
15	6, table 9	1:1 LAH:AlCl ₃ , NEt ₃	76	0.22
16	5, table 9	1:3 LAH:AlCl ₃ , NEt ₃	51	0.07

^a Migr. prod. = yield of TMBOH + amt. TMPOH-3 arising by the migration pathway

^b not determined

bination species present in this reagent will again be given¹⁵.

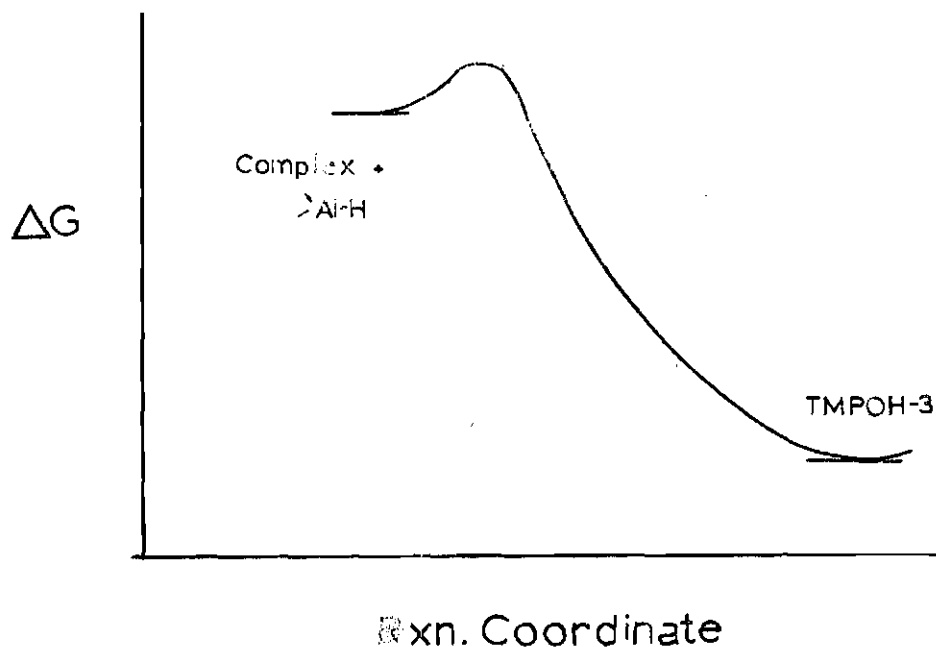


The product ratios from the reductions of β -diisobutylene oxide with the one to four and one to three lithium aluminum hydride to aluminum chloride combinations are essentially identical. This shows that aluminum chloride plays no role in determining the product ratios in this reduction (compare entries 4 and 5, Table 8). However, the complexed lithium chloride seems to play a fairly significant role. This is demonstrated by the following considerations: First of all, the product ratios from the reductions of β -diisobutylene oxide involving the one to three hydride to halide combination and pure hydridoaluminum dichloride are slightly different. This difference is well outside the range of experimental error, judging from the high reproducibility of the results. Furthermore, the ratio of the yield of trimethylbutanol-3 to that of tetramethylbutanol is almost twice as high from the reduction involving the one to three hydride to halide combination as it is from the case of the reduction involving pure hydridoaluminum dichloride (entries 7 and 9, Table 12). The ratio of the amount of trimethylpentanol-3 arising from direct reduction to the amount of products arising from migration and subsequent reduction in the case of the one to three hydride to chloride combination is more than twice as large as in the case from the reduction

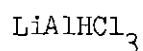
involving pure hydridoaluminum dichloride (entries 7 and 9, table 14). This indicates that the one to three hydride to chloride combination is a stronger reducing agent than is pure hydridoaluminum dichloride. This may seem at first glance like a small difference, and may be explicable solely in terms of a salt effect. However, this worker feels that the alternate explanation presented below is a more valid rationale for this effect, for the following reasons:

The reaction that determines the products is the reaction of the intermediate carbonium ion. This was discussed earlier. The ratios of trimethylpentanol-3 to tetramethylbutanol arising from reagents of similar acidity can be thought of as representing relative rates of direct reduction of the intermediate carbonium ion. Consider the transition state for this reaction:

Figure 3. Transition State for the Reaction of the Intermediate Carbonium Ion with a Hydride Donor.

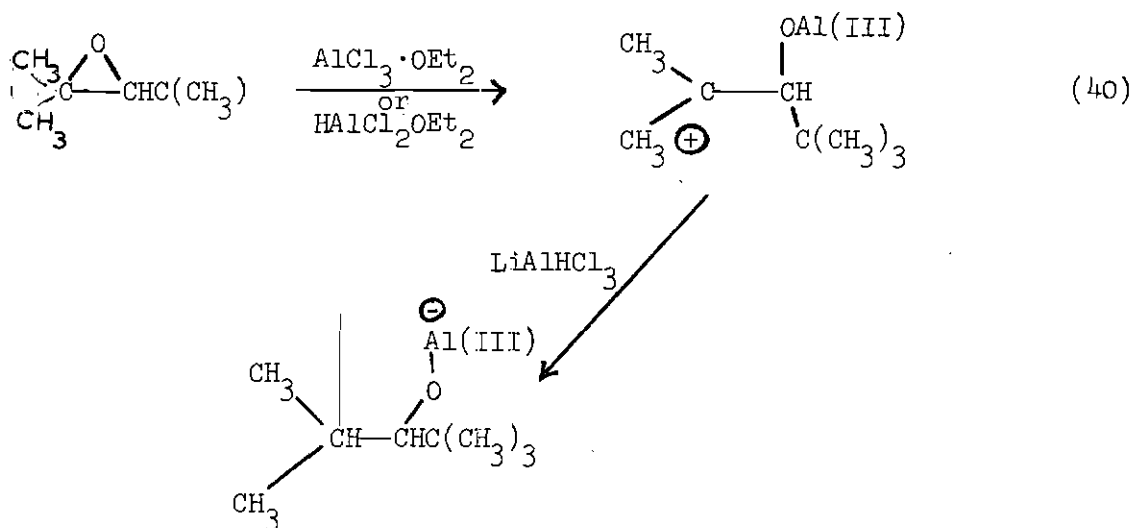


Since the reaction shown involves the transformation of a relatively free carbonium ion to an alcohol salt, it is obviously rather exothermic. The Hammond postulate states that for an exothermic reaction, the transition state more closely resembles starting material than products. Therefore, carbon-hydrogen bond formation from the reduction is probably not appreciable in the transition state. This, of course means that a carbonium ion is not very selective in its reactions with hydride donors. For reductions involving two reagents to exhibit a two-fold rate difference under these conditions indicates a significant difference in reducing power between the two reagents. The only difference in the one to three lithium aluminum hydride to aluminum chloride combination and hydridoaluminum dichloride is that the former contains lithium chloride, presumably complexed with hydridoaluminum dichloride¹⁵. This metastable complex has been assigned the formula shown below:



No spectral evidence could be obtained for its presence by the earlier workers, but its formation satisfactorily explains the fact that lithium chloride, normally insoluble in diethyl ether, does not precipitate when ethereal lithium aluminum hydride and aluminum chloride are mixed according to equations (19) and (20). The difference in reducing power between the one to three hydride to chloride combination, containing excess lithium chloride and the same reagent with lithium chloride removed, can be regarded as kinetic evidence for the existence

of the LiAlHCl_3 complex. It is evidently a more potent reducing agent than is $\text{HAlCl}_2 \cdot \text{OEt}_2$, as might be expected. Coordination of HAlCl_2 with a negatively charged species, such as chloride ion, would be expected to result in a higher electron density on the aluminum atom than would coordination of HAlCl_2 with a neutral species, such as diethyl ether. A higher electron density on the aluminum atom should result in increased reactivity as a hydride donor. The reductions of β -diisobutylene oxide involving the one to four and one to three reagents probably proceed by the following pathways:



The olefinic alcohol, 2,4,4-trimethylpenten-1-ol-3 (D-1-TMPOH-3) probably arises by internal elimination, as proposed by Zakharkin²⁴ rather than by an E_2 elimination as proposed by Rerick and Eliel²², at least in diethyl ether. Diethyl ether has never been noted for its ability to function as a basic catalyst for such a process.

This internal elimination occurs to a small but significant extent in virtually all of the mixed hydride reductions of β -diisobutylene oxide, as inspection of the data given in Tables eight through ten indicates.

A facet of this work which should be thoroughly discussed is the agreement of our data with that of past workers^{22,24}. Results from this work concerning reductions of β -diisobutylene oxide with the one to four lithium aluminum hydride to aluminum chloride reagent agree well with those obtained by earlier workers. However, the results from reductions of β -diisobutylene oxide involving the one to one and three to one lithium aluminum hydride to aluminum chloride mixtures performed in this laboratory are in poor agreement with the previous work²⁴ (compare entries 3 and 4, 6, and 7, and 11 and 12, Table 8). A possible reason for this which has not ruled out is that previous workers^{22,24} cooled their reaction mixtures in an ice bath while the epoxide solutions were added to the mixed hydride reagents. On the other hand our experiments were carried out at higher temperatures than those performed earlier. Another possible explanation for the difference in results was ruled out by the experimental evidence discussed below.

Elie and his coworkers^{11,12,22} prepared their reagents by adding ethereal lithium aluminum hydride to a mixture of aluminum chloride and ether at ice bath temperature. Mixed hydrides were prepared in this laboratory by mixing ethereal lithium aluminum hydride and aluminum halide solutions at room temperatures (ca. 25 or 26 degrees). It was considered possible that under our conditions of somewhat higher reaction temperatures during the preparation of the mixed

hydrides, the mixed hydride might be disproportionating, or that initial formation of aluminum hydride might be kinetically favored, and that aluminum hydride might be polymerizing and precipitating out of solution before it could redistribute with all of the aluminum chloride present. Both of these phenomena would result in the presence of mixed hydrides of higher Lewis acidity than anticipated or desired. These possibilities were examined and ruled out by preparing one to one lithium aluminum hydride to aluminum chloride mixtures at room temperature and at a lower temperature (see p. 47). Infrared analyses of these mixtures showed that they were identical in composition and consisted predominantly of dihydridoaluminum chloride as expected from consideration of the results of previous work on the chemistry involved in combining lithium aluminum hydride and aluminum halides in varying stoichiometric ratios. Furthermore the product ratios determined from analyses of the gross products from reductions performed on β -diisobutylene oxide by both of these reagents were essentially identical. This proves that the temperature at which hydride and halide solutions are mixed has no effect on the composition and reducing properties of mixed hydride reagents.

The previous workers have treated the commercially available anhydrous aluminum chloride essentially as a primary standard, i.e., they did not purify this material, or perform any analyses on any of the resulting reagents. It has been the experience of this worker that commercially available anhydrous aluminum chloride can deteriorate appreciably over a period of time, presumably through hydrate formation and partial hydrolysis. For this reason, aluminum chloride (and

iodide) were purified by sublimation prior to use, and aluminum chloride solutions were used as soon as possible after their preparation and standardization. It is this worker's belief that, since commercially available aluminum halides are of questionable purity, the past workers treatment of it as a primary standard resulted in the preparation of a mixed hydride of different properties than was intended. The actual ratios of lithium aluminum hydride to aluminum chloride are probably higher than those stated in the earlier publication²⁴. This would result in the reagents whose Lewis acidities were lower and reducing powers were enhanced compared to reagents whose actual ratios of hydride to halide is the same as those stated. This will be illustrated in the discussion of results from the reductions using the three to one lithium aluminum hydride to aluminum chloride reagent.

Inspection of the data (entry 12, Table 8) obtained from the reduction of β -diisobutylene oxide with this reagent shows that the product arising from the internal elimination tends to predominate to a much greater extent than it does in reactions involving other mixed hydride reagents. This can be rationalized in the following manner: aluminum hydride, the species present in the three to one reagent, is not a strong enough Lewis acid to sufficiently activate the epoxide toward reduction by aluminum hydride alone, an only moderately strong reducing agent. The oxirane ring is probably not completely cleaved, so migration cannot readily take place, i.e., direction reduction and migration and subsequent reduction are too slow under these conditions to compete favorably with internal elimination. If a stronger reducing agent were present in the aluminum hydride solution one

would expect direct reduction to become the predominant pathway. Data obtained from the reduction involving a four to one lithium aluminum hydride to aluminum chloride combination (containing AlH_3 and excess LiAlH_4) shows that this is indeed the case. Also, the results from the reduction of β -diisobutylene oxide with the four to one combination of lithium aluminum hydride to aluminum chloride are in good agreement with those of the reduction done in previous work²⁴ using a three to one combination (compare entries 10 and 14, Table 8). This is good evidence for the assertion made in the preceeding paragraph that the aluminum chloride used in the earlier work was contaminated, causing an excess in the ratio of hydride to halide over that stated. We feel that the three to one and one to one lithium aluminum hydride to aluminum chloride combinations prepared by the earlier workers actually were composed of mixtures of aluminum hydride with lithium aluminum hydride, and dihydridoaluminum halide with aluminum hydride respectively. This would explain the discrepancy in the results with the one to one and three to one lithium aluminum hydride to aluminum chloride mixtures.

A preliminary study of the reduction of 1-phenylcyclopentene oxide by aluminum hydride cited earlier showed that when excess aluminum hydride was used for the reduction, the predominant product is trans-2 phenylcyclopentanol¹⁶. However if excess epoxide is used, products that can be best rationalized by a migration and subsequent reduction arise predominantly³³. The explanation given for this was

33. P. T. Lansbury, private communication.

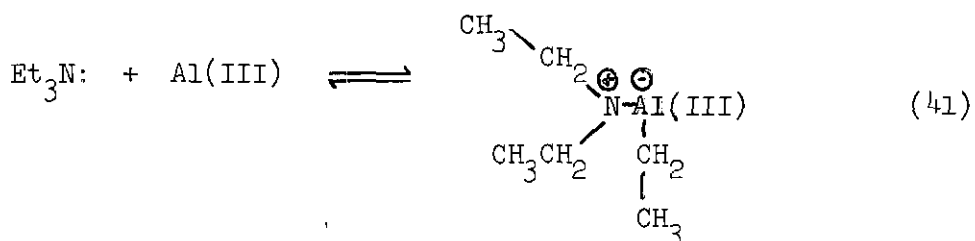
that the intermediate alkoxyaluminum hydrides were catalyzing the ring opening and migration. These alkoxy aluminum hydrides are the initial reduction products. The corresponding alcohols, the final products, arise from hydrolysis of the reaction mixtures. The properties of alkoxyaluminum hydrides were postulated to be very similar to those of the dihydridoaluminum halides.³³ However, recent work on the preparation and characterization of alkoxy aluminum hydrides, and our work with these compounds, which will be discussed later, indicate that this is not the case²⁰. The shift to migration from direct reduction as the predominant pathway as the ratio of reducing species to epoxide is decreased can also be thought of as a concentration effect. The kinetic expression for the rate of direct reduction pathway for reductions of epoxide involving aluminum hydride is probably overall third order, and second order in aluminum hydride. That for the migration pathway would be overall second order, and first order in aluminum species. According to these arguments, it would be expected that if an excess of aluminum hydride over the epoxide is used in the reduction, products arising from the higher order process should predominate. If the ratio of hydride to epoxide is decreased, products arising from the lower order process should tend to predominate. This was exactly what was observed in the reductions of the above cyclic epoxide. Reductions involving the one to one and three to one lithium aluminum hydride to aluminum chloride were performed on β -diisobutylene oxide in this laboratory using two different hydride to epoxide ratios. For the reductions involving the one to one combination, molar ratios of dihydridoaluminum chloride to epoxide of 1.5 to one and three to

one' were used (entries 7 and 10, Table 8). The relative amounts of direct reduction products is slightly higher in the gross product of the latter reduction than it is in the former, but the trend is slight. The two molar ratios of aluminum hydride to epoxide used in the reductions involving the three to one combination were three to one and one to one (entries 13 and 11, Table 8). If alkoxyaluminum hydrides had the same type of properties as hydrido-aluminum halides and participated in the reductions it would be expected that migration might tend to be the prevalent pathway in the aluminum hydride reduction of β -diisobutylene oxide where the molar ratio of hydride species to epoxide is one to one. The alkoxyaluminum hydrides evidently are not strong enough Lewis acids to catalyze migration, since as was stated before, internal elimination is the prevalent pathway in this reaction, rather than migration. It therefore seems likely that alkoxyaluminum hydrides do not play a role in the mixed hydride reductions of β -diisobutylene oxide, presumably due to their steric bulk and lack of Lewis acidity. However, the aluminum hydride reduction of β -diisobutylene oxide using a molar ratio of hydride species to epoxide of three to one, direct reduction competes quite favorably with internal elimination as examination of the product ratios (entry 13, Table 8) indicates. This is just the type of concentration effect that would be expected from a consideration of the mechanism postulated above.

The results arising from reductions involving mixed hydride reagents prepared as etherates from lithium aluminum hydride and aluminum chloride have now been discussed in a fairly thorough manner.

The work involving reductions by mixed hydrides as tetrahydrofuran and triethylamine solvates should now be discussed briefly. It would be expected that solvates of these types would be stronger reducing agents than the corresponding mixed hydrides as diethyl etherates, because the above solvating species are probably better electron donors than diethyl ether. The reductions involving a mixed hydride as the tetrahydrofuranate or triethylamminate should yield a higher ratio of direct reduction product yields to migration and elimination product yields than a reduction by the same mixed hydride as the diethyl etherate. This was found to be the case with the tetrahydrofuranates as examination of the data in tables eight, nine, twelve and thirteen illustrates.

The results from reductions, involving mixed hydrides as triethylamminates cannot be explained in such a straightforward manner. In the first place, tertiary amines have long been known to be weaker bases than secondary amines.³⁴ This is presumably a steric effect resulting from crowding of the three alkyl groups in the quaternary ammonium salt shown in equation (41) below, which would force the equilibrium shown more to the left.



³⁴. H. C. Brown and H. Bartholomay, Jr., M.S. Taylor, J. Am. Chem. Soc., 66, 435 (1944).

This would leave more trivalent aluminum species available for complexation with epoxide than would be expected if a less bulky base were used. Also, the triethylamine complexes of mixed hydride reagents are fairly bulky. It would be expected that their reducing power would be diminished by steric effects. If the results from reductions using the triethylamminates and diethyletherates of the one to three (entry 5, Table 8; entry 4, Table 9) one to one (entry 7, Table 8; entry 6, Table 9) and three to one (entry 12, Table 8; entry 7, Table 9) lithium aluminum chloride reagents are examined, the following trends are noticeable: First of all, for the one to one and one to three combination, there is little difference in the product ratios from reductions of β -diisobutylene oxide involving these reagents as the diethyletherates or triethylamminates. This could be attributed to the effect of substituting relatively bulky chlorines for hydrogen in aluminum hydride triethylamminate, which would make a progressively even more bulky reducing species. This is partly corroborated by the fact that aluminum hydride triethylamminate, unlike the hydridoaluminum chloride triethyl amminates is a stronger reducing agent than the corresponding mixed hydrides as the diethyl etherate, judging from the TMPOH-2/TMPOH-3 ratios plotted in table 13. Another fact that should be noted is that the olefinic side product, 2,4,4-trimethylpenten-1-ol-3, probably arises via an E_2 elimination if uncomplexed triethylamine is present. This is shown by the following data. Two reductions of β -diisobutylene oxide by a one to three lithium aluminum hydride to aluminum chloride combination

to which triethylamine has been added were carried out. One reduction mixture was prepared by adding an amount of triethylamine equivalent to the hydridoaluminum halide present. The other was prepared with a two-fold molar excess of triethylamine. The gross product from the latter reduction contained significantly more elimination product than the former (compare entries 4 and 5, Table 9).

Some facets of the reduction using mixtures of lithium aluminum hydride and aluminum bromide or iodide have already been discussed. Some of these will now be reviewed and additional information will be presented.

First of all it would be expected that mixed hydrides prepared from aluminum bromide would exhibit less Lewis acidity, and consequently greater reducing power than the corresponding reagents prepared with aluminum chloride. Evidence presented in tables eight, ten, twelve and thirteen which has already been discussed in part show that this is the case. However, some of the results for reductions involving mixed hydrides prepared with aluminum iodide do not follow the expected trends. The one to three lithium aluminum hydride to aluminum iodide combination is seen to be a relatively potent reducing agent (entry 3, Table 10). In fact the product ratios from the reduction with this reagent most closely resemble those from the reduction involving the one to one lithium aluminum hydride-aluminum chloride combination (entry 7, Table 8), the only significant difference being a higher yield of the olefinic alcohol in the gross product from the iodide reagent than in the chloride reagent. The results from the

reduction involving the one to one lithium aluminum hydride-aluminum iodide are anomalous (entry 4, Table 10). In the first place, no significant amount of trimethylpentanol-2 could be detected in the product. Secondly the yield of olefinic alcohol is higher than usual for this type of reagent. This could perhaps be explained in the following manner:

The Lewis acidity of this reagent is probably not much higher than that of aluminum hydride since iodine is not very electron-negative. The reducing power of the reagent relative to that of aluminum hydride would be less, partially due to electronic factors but probably predominantly due to the increase in steric hindrance expected in substituting an iodine for a hydrogen. This could explain the increase yield of the product of internal elimination. Hydridoaluminum diiodide, the species present in the one to three lithium aluminum hydridoaluminum iodide combination is evidently a strong enough Lewis acid to activate the epoxide sufficiently so that it can react with the very bulky reducing agent present at a rate significantly faster than internal olefin formation can occur. Also internal olefin elimination would be more favorable statistically in reductions involving the one to one iodine containing reagent than in the one to three iodine containing reagent. There are two aluminum bound hydrogens in the former but only one in the latter.

The results from the reductions of β -diisobutylene oxide by the various alkoxyaluminum hydrides will now be presented. A few preliminary remarks about the properties of the various alkoxyaluminum

hydrides should be made before the results are discussed.

As stated earlier, alkoxyaluminum hydrides have been postulated as reactive intermediates in the reduction of epoxides by certain mixed hydrides³³, and also by lithium aluminum hydride alone³⁵ under certain conditions. These reagents have been stated to have properties similar to those of the hydridoaluminum halides; i.e., they have been postulated to be fairly potent Lewis acids. Recent work has shown that these alkoxyaluminum hydrides have very different properties than the mixed hydride species. This will be explained.

The hydridoaluminum halides have been shown in work already cited to be monomeric in diethyl ether. The methoxy- and t-butoxyaluminum hydrides are all associated in tetrahydrofuran. Dimethoxyaluminum hydride, which results when aluminum hydride and methanol are mixed in any stoichiometric ratio is a polymeric species insoluble in all common aprotic solvents. Di-t-butoxyaluminum hydride is a dimer in this solvent and mono-t-butoxyaluminum hydride is either a dimer, or a trimer, depending on the circumstances.

35. R. Fachs and C. A. VanderWerf, J. Am. Chem. Soc., **74**, 5917 (1952).

Table 15. Product Ratios from the Reduction of β -diisobutylene Oxide by Various Alkoxyaluminum Hydrides^a

entry no.	reducing agent	epox. (%)	gross prod. yield (%)	TMPOH-2	TMPOH-3	Δ -1-TMPOH-3	TMBOH
1	AlH_3^b	-	65-100	30	69	1	-
2	$\text{AlH}_2\text{Ot-Bu}^{b,c}$ (normal)	47-64	12-24	28	59	10	3
3	$\text{AlH}_2\text{Ot-Bu}$ (forcing)	25	52	7	25	59	9
4	$\text{AlH}(\text{Ot-Bu})_2$ (normal)	65-77	2	d	d	d	d
5	$\text{AlH}(\text{Ot-Bu})_2$ (forcing)	35	51	1.5	2.4	90	6
6	$\text{AlH}_2\text{Oi-Pr}$ (normal)	58	16	28	49	17	6
7	$\text{AlH}_2\text{Oi-Pr}$ (forcing)	-	76	19	45	33	3
8	$\text{AlH}(\text{Oi-Pr})_2$ (normal)	58	1 ^e	29	29	14	29
9	$\text{AlH}(\text{Oi-Pr})_2$ (forcing)	2	9 ^e	9	3	73	15
10	AlH_2OMe^b	13-18	63-67	23	67	3	2
11	$\text{AlH}(\text{OMe})_2$ (normal)	64	2 ^e	23	20	30	27
12	$\text{AlH}(\text{OMe})_2$ (forcing)	50	4 ^e	22	14	60	14

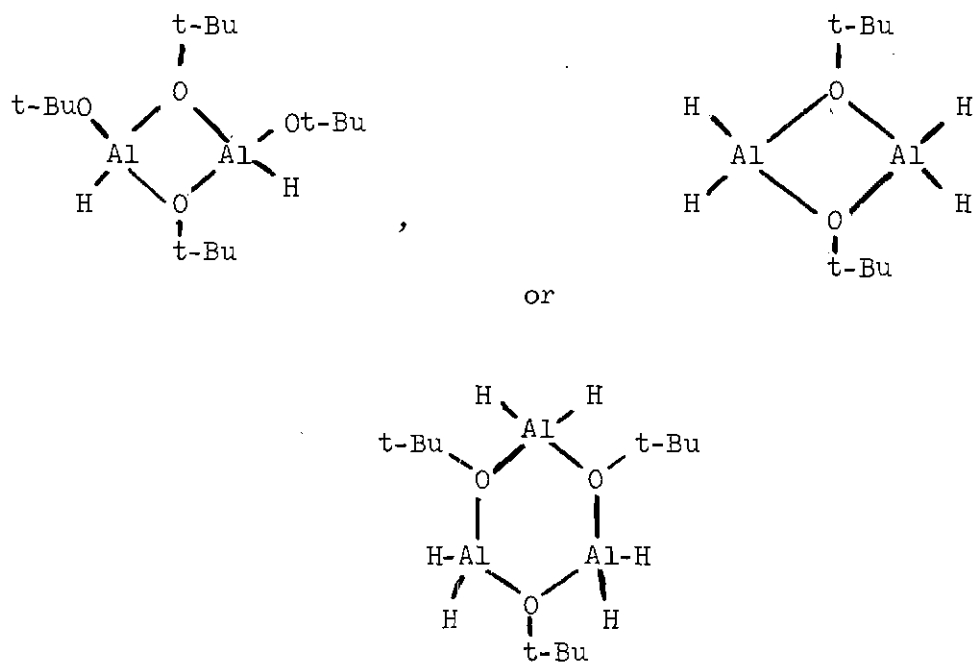
^athree equivalents hydride per mole epoxide; Only one run was made, unless otherwise stated.

^baverage of two runs.

^caverage deviation of plus or minus four or five absolute percent for each component.

^dTwo runs were made, but the results from each run were in poor agreement. This is presumably due to the low extent of reaction of β -diisobutylene oxide with this alkoxyaluminum hydride.

^eOnly one run was made. The extent of reaction is so low that the product ratios are only accurate to about 10 or 15 percent.

Figure 4. Mono and Di-*t*-butoxyaluminum Hydride

All of the species studied were found to be associated through alkoxy bridging groups²⁰. It stands to reason that a fairly basic solvent, such as tetrahydrofuran, cannot cleave these bridge bonds to an extent that would be measurable in an association study then neither could an epoxide such as β -diisobutylene oxide. Complex formation and the resulting activation toward reduction would not take place to nearly the extent in these reactions that they take place in mixed hydride reductions. This is shown by the fact that none of the reductions of β -diisobutylene oxide by alkoxyaluminum hydride goes to completion, not even those run under forcing conditions. That this is not merely a solvent effect is shown by the fact that the reduction involving aluminum hydride in tetrahydrofuran is complete within two hours at

room temperature. Also since they are associated they should be relatively unreactive as reducing agents, because of their rather considerable bulk. The results from the reductions of β -diisobutylene oxide with the dialkoxyaluminum hydrides are inconclusive because the reactions take place to such a limited extent under the conditions used. About the only trend that can be noted is that the yield of 2,4,4-trimethylpentene-1-ol-3 is significantly higher for the reductions run under forcing conditions than for those run under normal conditions (compare entries 4 and 5, and 8 and 9, Table 14). The same type of difference was noted for reductions of β -diisobutylene oxide with aluminum hydride in ether run under normal and forcing conditions²⁴.

The results from the reductions involving the alkoxyaluminum dihydrides are somewhat more informative. The ratios of the yields of trimethyl pentanol-2 to trimethylpentanol-3 is fairly high for the reductions involving both the isopropoxy and t-butoxyaluminum dihydride, run under normal conditions, indicating that these reagents are only poor Lewis acids. (The "monomethoxyaluminum hydride", prepared by adding one mole of methanol to one mole of aluminum hydride actually consists of polymeric, solid dimethoxyaluminum hydride and aluminum hydride in solution, and the results from the reduction of β -diisobutylene oxide with this reagent are meaningless in this series). However if these reductions are run under forcing conditions the following trends are noted. First of all, relative yields of the olefinic alcohol are higher in the reductions run under forcing conditions than those run under normal conditions (compare entries 2 and 3

and entries 6 and 7, Table 14). Secondly the ratios of the yields of trimethylpentanol-2 to trimethylpentanol-3 is lower for the reductions run under forcing conditions than for the corresponding reductions run under normal conditions (see Table 16).

Table 16. Ratios of TMPOH-2 to TMPOH-3 from the Reductions of β -diisobutylene Oxide by Monoalkoxyaluminum Hydrides.

Entry no.	Entry no. from Table 14	Reducing agent	TMPOH-2/TMPOH-3
1	2	$\text{AlH}_2\text{Ot-Bu}$ (normal)	0.47
2	3	$\text{AlH}_2\text{Ot-Bu}$ (forcing)	0.28
3	6	$\text{AlH}_2\text{O-i-pr}$ (normal)	0.57
4	7	$\text{AlH}_2\text{O-i-pr}$ (forcing)	0.42

This can possibly be explained by assuming that two direct reduction pathways are competitively involved. One, an acid assisted Sn_2 pathway, involving an attack by the reducing species on an activated epoxide alkoxyaluminum hydride complex, and the other involving an Sn_2 attack by the reducing species on uncomplexed epoxide. Judging from the TMPOH-2/TMPOH-3 ratios given in Table 16, the former pathway probably predominates even under normal conditions. In reductions run under forcing conditions, the epoxides or the solvent might be better able to cleave the alkoxy bridging bonds than they are at lower temperatures. If this were the case complex formation would be expected to occur to a

greater extent at the higher temperature. This being true, it would be expected that the pathway involving attack of complexed epoxide by the reducing species would be more prevalent at higher temperature than lower temperature. Electronic effects on relative product yields from direct reduction would assume increasing importance relative to steric effects. A great deal more experimental evidence is needed before this hypothesis can be considered as proved, but it does explain the results.

A great deal of additional work needs be done on the reductions of epoxides with alkoxyaluminum hydrides. One of the first things that comes to mind is to perform these reductions on a less sterically hindered, and more reactive epoxide, such as styrene oxide and/or isobutylene oxide and compare these results with those obtained from mixed hydride reductions, and the reduction using lithium aluminum hydride alone performed on the same epoxides. It is the feeling of this worker that alkoxyaluminum hydrides are more similar to lithium aluminum hydride than to the mixed hydrides, as far as reducing power is concerned. Results from reductions performed on the above less sterically hindered epoxides should either prove or disprove this contention.

This concludes the discussion of these results. The following chapter deals with sample calculations of product ratios from some of the reductions of styrene oxide and β -diisobutylene oxide. Vapor phase chromatographic data from each type of reduction will be presented in tabular form.

CHAPTER VII

APPENDIX AND SAMPLE CALCULATIONS

The raw VPC data from the reductions of β -diisobutylene oxide will now be presented in tabular form. This will be followed by an attempt to derive any relationships whose origins were not made clear in the body of this thesis, and illustrations on how the product ratios and material balances were calculated. The calculation of the relative migratory aptitudes of hydrogen and tert-butyl will be presented, as will a sample calculation illustrating how the ratios of yields of trimethylpentanol-3 (TMPOH-3) arising from direct reduction to total yield of migration products were obtained.

Table 17. VPC Data From Reductions of β -diisobutylene Oxide by Various Combinations of LiAlH_4 and AlCl_3 .

entry no.	ratio of $\text{LAH}:\text{AlCl}_3$	TMPOH-2 area ^a	TMPOH-3	Δ -1-TMPOH-3 area	TMBOH area	n-oct area
2	LAH alone	-	-	-	-	-
4	1:4	0.02	0.41	0.21	1.86	2.76
5	1:3	0.03	0.33	0.16	1.49	2.16
7	1:1	0.06	0.57	0.17	1.50	2.30
8	1:1, L.T.	0.05	0.44	0.16	1.00	1.34
9	1:1, R.T.	0.04	0.40	0.16	1.08	1.50
10	1:1	0.08	0.90	0.17	1.72	2.40
12	3:1	0.21	0.60	0.74	0.13	1.70
13	3:1	0.25	0.72	0.29	0.06	1.18
14	4:1	0.41	0.85	0.15	0.04	1.27
15	HAlCl_2	0.03	0.15	0.12	1.15	0.67

^a in square inches

The entry numbers in this table coincide with these in table 8 above.

Table 18. VPC Data from Reductions of β -diisobutylene Oxide by Lithium Aluminum Hydride-Aluminum Chloride Combinations as Tetrahydrofuranates and Triethylamminates.

entry no.	ratio of LAH:AlCl ₃	TMPOH-2 area ^a	TMPOH-3 area	Δ -1-TMPOH-3 area	TMBOH area	n-octanol area
1	1:3, THF	0.03	0.33	0.11	0.75	1.23
2	1:1, THF	0.21	0.99	0.13	0.62	1.14
3	3:1, THF	0.29	0.56	0.08	0.004	0.50
4	1:3, NEt ₃	-	0.21	0.27	1.22	0.96
5	1:3, NEt ₃	-	0.10	0.45	0.64	1.51
6	1:1, NEt ₃	0.025	0.43	0.32	1.30	1.30
7	3:1, NEt ₃ ^b	0.22	0.47	0.31	0.03	0.86

^ain square inches

^bA peak area of 0.45 square inches due to starting material was also observed.

Entry numbers in this table coincide with those in Table 9.

Table 19. VPC Data from Reductions of β -diisobutylene Oxide by Various Lithium Aluminum Hydride-Aluminum Bromide or Iodide Combinations.

entry no.	ratio of LAH:AlX ₃	TMPOH-2 area ^a	TMPOH-3 area	Δ -1-TMPOH-3 area	TMBOH area	n-octanol area
1	1:3, Br	0.015	0.37	0.27	1.35	1.75
2	1:1, Br	0.06	0.79	0.12	0.79	1.54
3	1:3, I	0.04	0.58	0.42	1.28	1.35
4	1:1, I	-	0.42	0.42	0.44	0.63

^ain square inches

Entry numbers in this table coincide with those given in Table 10.

Table 20. VPC Data from Reductions of β -diisobutylene Oxide by Various Alkoxyaluminum Hydrides.

entry no.	reducing agent	epoxide area ^a	TMPOH-2 area	TMPOH-3 area	Δ -1-TMPOH-3 area	TMBOH area	n-oct. area
1	AlH_3	-	0.19	0.46	0.04	-	0.34
2	$\text{AlH}_2\text{O-t-Bu}$ (normal)	3.68	0.19	0.34	0.11	0.03	1.84
3	$\text{AlH}_2\text{O-t-Bu}$ (forcing)	0.36	0.05	0.19	0.45	0.07	1.11
4	AlH(O-t-Bu)_2 (normal)	3.76	0.01	-	0.03	-	1.54
5	AlH(O-t-Bu)_2 (forcing)	1.16	0.025	0.04	1.40	0.09	1.53
6	$\text{AlH}_2\text{O-i-Pr}$ (normal)	1.72	0.13	0.23	0.07	0.03	2.28
7	$\text{AlH}_2\text{O-i-Pr}$ (forcing)	-	0.25	0.61	0.41	0.04	1.25
8	AlH(O-i-Pr)_2 (normal)	1.60	0.01	0.005	0.01	0.01	2.13
9	AlH(O-i-Pr)_2 (forcing)	1.40	0.02	0.008	0.16	0.035	2.12
10	AlH_2OMe	0.32	0.31	0.77	0.03	0.03	1.86
11	AlH(OMe)_2 (normal)	1.36	0.013	0.011	0.015	0.015	1.63
12	AlH(OMe)_2 (forcing)	0.72	0.011	0.007	0.03	0.007	1.09

^ain square inches.

The entry numbers in this table coincide with those in Table 11

The method of calculation of data for the reductions of styrene oxide involving the mixed hydrides will now be illustrated. The data used arose from the reduction of styrene oxide by the one to four hydride to halide combination (entry 3, table 7).

$$\text{area under peak due to styrene oxide} = 0.5 \text{ in.}^2$$

$$\text{area under peak due to 1-phenylethanol} = 0.04 \text{ in.}^2$$

$$\text{area under peak due to 2-phenylethanol} = 2.42 \text{ in.}^2$$

$$\text{area under peak due to n-octanol} = 4.24 \text{ in.}^2$$

$$\text{wt. of n-octanol used as internal standard} = 0.797 \text{ g.}$$

(see p. 42)

$$Z(\text{styrene oxide/n-octanol}) = 1.22$$

$$Z(\text{1-phenylethanol/n-octanol}) = 1.12$$

$$Z(\text{2-phenylethanol/n-octanol}) = 1.22$$

(see table 3, p. 35)

$$\text{amount of styrene oxide used in this reduction} = 7.15 \text{ mmoles}$$

(see p. 42)

Substitution of this data into equation 37 (see p. 34, and preceeding discussion) yields the following relationships and results:

$$\text{wt. styrene oxide} = Z(\text{oct./styrene oxide}) \times \dots$$

$$\frac{\text{wt. oct.} \times A \text{ styrene oxide}}{A \text{ oct.}}$$

$$= 1.22 \times \frac{0.797 \times 0.5}{4.24} \text{ g.}$$

$$= 0.115 \text{ g. or } 0.953 \text{ meq.}$$

$$\text{wt. 1-phenylethanol} = 1.12 \times \frac{0.797 \times 0.04}{4.24} \text{ g.}$$

$$= 0.084 \text{ g. or } 0.069 \text{ meq.}$$

$$\text{wt. 2-phenylethanol} = 1.22 \times \frac{0.797 \times 2.42}{4.24} \text{ g.}$$

$$= 0.555 \text{ g. or } 4.53 \text{ meq.}$$

$$\text{total meq of alcoholic products} = 4.60$$

$$\% \text{ yield of alcoholic products} = \frac{4.60 \text{ meq} \times 10^2}{7.15 \text{ meq}} = 64\%$$

$$\text{1-phenylethanol/2-phenylethanol} = 0.69/4.60 : 4.53/4.60 = 2:98$$

$$\% \text{ recovery of starting material} = \frac{0.953 \times 10^2}{7.15} = 13\%$$

The method of calculation of the product ratios from the V.P.C. data obtained from mixed hydride reductions of β -diisobutylene oxide will now be presented. Inspection of the results from Table 6 (see p. 38) shows that for three of the four products, the product ratios and material balances can be calculated directly by comparing the areas under the appropriate peaks. This follows intuitively from the following facts:

$$Z_{(\text{oct.}/\text{TMPOH-2})} = Z_{(\text{oct.}/\text{TMPOH-3})} = Z_{(\text{oct.}/\text{TMPOH})} \cong 1$$

(see table 6, p. 38)

However, this is not the case for the olefinic alcohol, 2,4,4-trimethylpenten-1-ol-3 (Δ -1-TMPOH-3):

$$Z_{(\text{oct.}/\Delta\text{-1-TMPOH-3})} = 1.08$$

The area obtained by integrating the peak on the chromatogram can be corrected so that the resultant area can be used directly in calculations of product ratios and material balances. This will now be illustrated.

The following data is taken from Table 17, entry 13.

$$A_{\text{TMPOH-2}} = 0.21 \qquad A_{\Delta\text{-1-TMPOH-3}} = 0.74$$

$$A_{\text{TMPOH-3}} = 0.60 \qquad A_{\text{TMPOH}} = 0.13$$

$$A_{\text{oct.}} = 1.70$$

$$A'_{\Delta\text{-1-TMPOH-3}} = 1.08 \times 0.74 = 0.80$$

$$\epsilon A_{\text{prod.}} = 1.74$$

Product ratios are calculated in the following manner:

TMPOH-2:

TMPOH-3:

$$\frac{A_{\text{TMPOH-2}} \times 10^2}{\epsilon A_{\text{prod.}}} = \frac{0.21 \times 10^2}{1.74} = 12 \qquad \frac{0.60 \times 10^2}{1.74} = 34$$

$\Delta\text{-1-TMPOH-3}$:

TMBOH:

$$\frac{0.80 \times 10^2}{1.74} = 46 \qquad \frac{0.13}{1.74} = 8$$

The gross product yields are calculated in the following manner:

$$\frac{\epsilon A_{\text{prod}} \times \text{wt. oct.} \times 10^2}{A_{\text{oct}} \times \text{wt. epoxide}} = \frac{1.74 \times 0.462 \times 10^2}{1.70 \times 0.500} = 95\%$$

(wt. oct. was taken from p. 46)

Data from a replicate run yields the following data:

TMPOH-2	TMPOH-3	$\Delta\text{-1-TMPOH-3}$	TMBOH
11	35	45	9

The gross product yield from this run was 100 percent. The averages of the product ratios is presented in entry 13 of table 8 (see p. 68).

The calculations of (TMPOH-2/TMPOH-3) and (TMPOH-3/TMBOH), presented in Tables 11 and 12, respectively, are performed by carrying out the indicated divisions using the product ratio data from Tables eight

through ten. These are too trivial to be illustrated by sample calculations.

The relative migratory aptitudes of hydrogen and the tert-butyl group were calculated from the NMR data obtained from the deuterated 2,4,4-trimethylpentanol-3 arising from the reduction of β -diisobutylene oxide with the one to three lithium aluminum deuteride to aluminum chloride combination. The data pertinent to the calculations are taken from Tables 8 and 13:

product ratios for TMPOH-3 and TMBOH (entry 16, Table 8):

TMPOH-3 : 11

TMBOH : 8

Integration peak heights from Table 13:

hydroxyl proton = 1.0

proton on carbon-bearing the hydroxyl group = 0.5-0.6

It can be seen that about half the 2,4,4-trimethylpentanol arises from a hydride shift and subsequent reduction (see chapters I and VI). The relative migratory aptitudes of H and tert-butyl can be calculated from the product ratios in the following manner:

entry 5, Table 8:

TMPOH-3 (product ratio) = 16

TMBOH (product ratio) = 74

TMPOH-3 arising from migration = [TMBOH] \times 0.076 = 74 \times 0.076 =
5.6

$$\frac{\text{TMPOH-3 direct reduction}}{\text{TMPOH-3 total}} = \frac{(16-5.6) \times 10^2}{16} = 65\%$$

This result is presented in Table 14, entry seven.

The straightforward calculation at the ratio of the amount of 2,4,4-trimethylpentanol-3 arising from direct reduction to the amount of products arising from migration and subsequent reduction is illustrated below:

$$\frac{\text{TMPOH-3 dir. red.}}{\text{migration products}} = \frac{\text{TMPOH-3 dir. red.}}{\text{TMPOH-3 migration} + \text{TMBOH}}$$

Substitution the appropriate data from the reduction of β -diisobutylene oxide involving the one to three hydride to chloride combination discussed above yields the following result.

$$\frac{\text{TMPOH-3 dir. red.}}{\text{Migration Prod.}} = \frac{16.0-5.6}{74 + 5.6} = 0.13$$

This result is presented in Table 14, entry seven.

This concludes the presentation of derivations and sample calculations.

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